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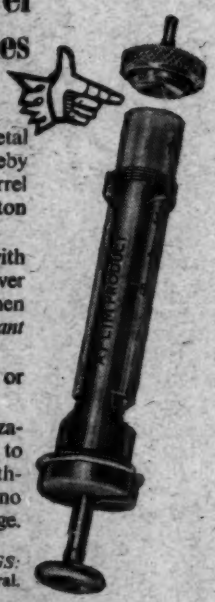

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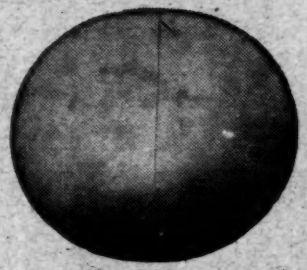

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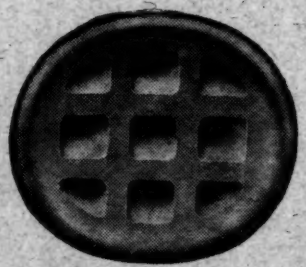

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 28 1953

ELECTROPHORESIS OF HUMAN GASTRIC JUICE IN RELATION TO CASTLE'S INTRINSIC FACTOR

BY

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AND

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From the Departments of Pathology and Medicine, King's College, University of Durham, and the Royal Victoria Infirmary, Newcastle-upon-Tyne

In the period 1929–37 Castle and his colleagues showed that normal gastric juice (intrinsic factor) administered orally to patients with pernicious anaemia would potentiate the haemopoietic effect of beef muscle (extrinsic factor). Later they showed that the extrinsic factor in beef muscle was vitamin B_{12} or a related compound (Gardner *et al.*, 1949), and that vitamin B_{12} itself behaved like extrinsic factor when small doses were administered orally (Berk *et al.*, 1948). Meanwhile there were many unsuccessful attempts to isolate Castle's intrinsic factor, which is heat-labile and readily inactivated by chemical procedures (see Ungley, 1951–2; Welch and Heinle, 1951; Welch and Nichol, 1952).

The methods employed in the present study were mainly physico-chemical: ultrafiltration and freeze-drying followed by preparative electrophoresis on filter paper. The techniques used were devised by one of us (A. L. L.). The method of electrophoresis has already been demonstrated (Latner *et al.*, 1952).

METHODS

These are the methods finally adopted. Their development from earlier ones is described below.

Acid gastric juice was collected from students and patients after stimulation with histamine or aminoethyl pyrazole dihydrochloride. The juice was neutralized and stored at approximately –20° C. Ultrafiltration was carried out at 0–5° C. Then the ultrafiltrate residuum was freeze-dried and reconstituted with buffer so that the gastric juice had been concentrated 150–200 times.

The filter paper used for electrophoresis was Whatman No. 31 extra thick. Each of the six strips was subdivided into 25 segments 1 cm. wide. The ultrafiltrate residuum from 500 to 800 ml. of gastric juice was applied with a paintbrush to these six strips so that each contained an approximately equal amount. After electrophoresis, separation of liquid from the segments by centrifuging gave 25 fractions labelled from 1 to 25, starting at the cathode end. A barbitone buffer at *p*H 8.6, used initially, was later replaced by a buffer at *p*H 6.35.

To test their vitamin B_{12}-binding power as a basis for grouping fractions for clinical trial, samples of 0.1 ml. from each fraction were added to 1 ml. of a solution containing 200 μg. vitamin B_{12}. Any vitamin left unbound was then estimated by plate assay using *Bact. coli* (Bessell, Harrison, and Lees, 1950). Fig. 3 shows vitamin B_{12}-binding peaks demonstrated in this way. (Figs. 1 and 2 relate to some preliminary observations in which vitamin B_{12} was added before electrophoresis.) Later, a method used for staining protein was found equally effective for the grouping of fractions (see Experiment E).

Clinical Trials

Tests were conducted in 15 cases of pernicious anaemia. Methods are described elsewhere (Ungley and Campbell, 1949; Ungley, 1950), but certain points need re-emphasis. The diet was restricted to reduce the intake of extraneous haemopoietic factors, particularly vitamin B_{12}. Food was withheld for at least six hours before and after the administration of test material. Test material was given orally as a single dose with 50 μg. vitamin B_{12}. The administration of vitamin B_{12} with a possible source of intrinsic factor was preceded by a test in which an equal dose of vitamin B_{12} was admin-

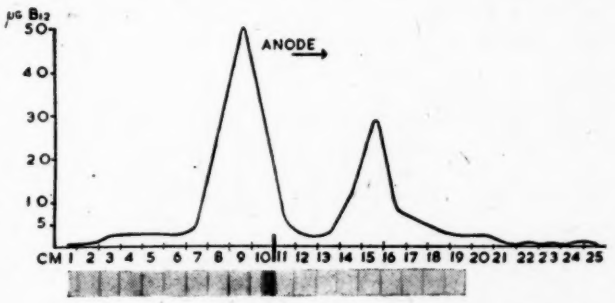

FIG. 1.—Tests on fractions obtained by electrophoresis (in barbitone buffer) of gastric juice concentrated 20 times: the curve shows two B_{12}-binding peaks. Shown below is a strip of paper stained for protein. The thick line on the abscissa represents the point of application of the material.

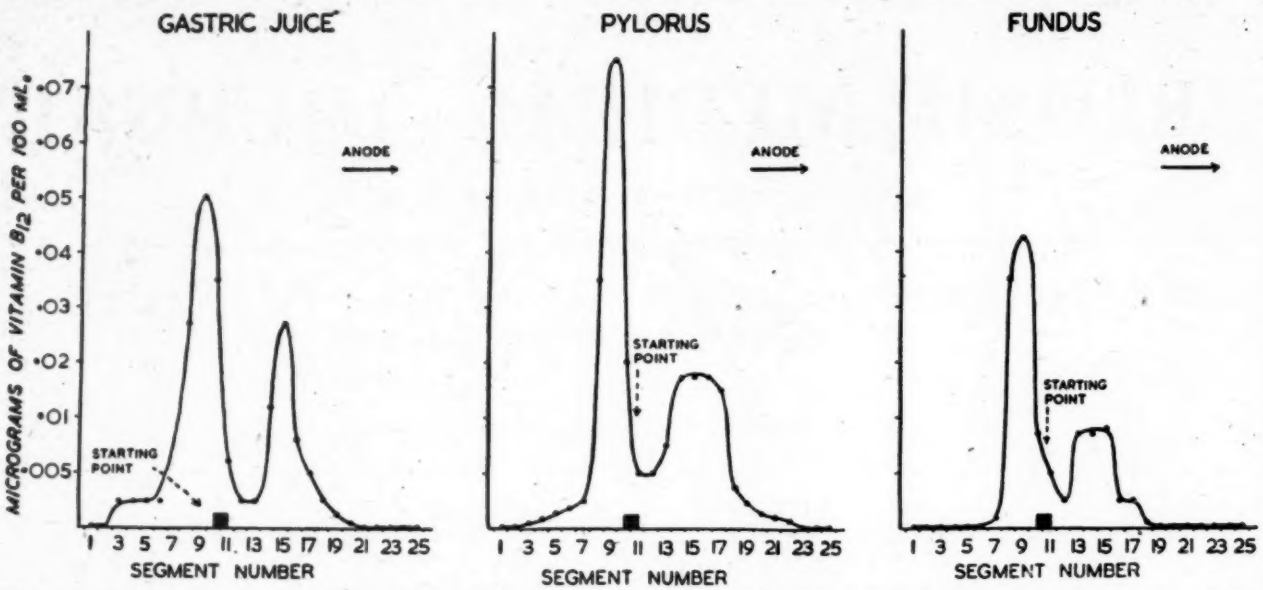

FIG. 2.—Results of simultaneous electrophoresis (in barbitone buffer) of gastric juice and extracts of pylorus and fundus mucosa of pig's stomach. Two vitamin B_{12}-binding peaks are shown in each case.

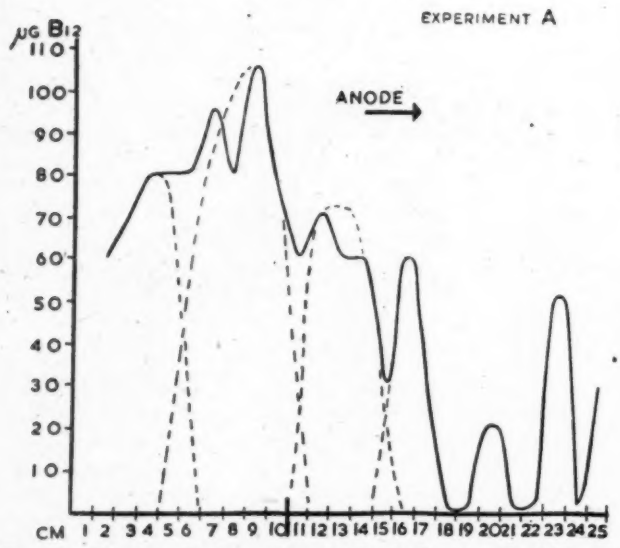

FIG. 3.—Results of electrophoresis (in buffer at *p*H 6.35) of gastric juice used in Experiment A. Vitamin B_{12} was added after electrophoresis, and the vitamin B_{12} bound by each fraction was determined. The thick line on the abscissa indicates the point of application of material.

istered alone or with an inactive fraction. A second test was not begun until any haemopoietic response initiated in the previous period had ceased: reticulocyte counts were <2%, serial estimations of red blood cells (R.B.C.), haemoglobin (Hb), and packed cell volume (P.C.V.) were level or falling, and the marrow was megaloblastic. A further point—namely, the use of one rather than several subjects for the comparison of fractions derived from one electrophoresis—is mentioned later.

Haematological Methods

Reticulocytes were counted daily by a wet method. Multiple determinations (usually two to five) of R.B.C., Hb, and P.C.V. were made every three to five days. Only mean values determined at five-day intervals are recorded here. Reticulocyte responses were observed, but were used only as an indication of the presence or absence of activity. For the quantitative evaluation of haemopoietic responses the rate of increase of R.B.C. and P.C.V. in 15 days was expressed in terms of the number of micrograms of injected vitamin B_{12} which would be expected to produce a similar response (Ungley and Campbell, 1949, and unpublished).

PRELIMINARY OBSERVATIONS

In an early study gastric juice was concentrated 20 times by ultrafiltration and vitamin B_{12} was added to the concentrate. Fig. 1 indicates the amounts of bound vitamin B_{12} in each of the 25 fractions obtained by subsequent electrophoresis.

Two peaks of vitamin B_{12}-binding can be seen—one on the cathode side near the starting-point and one on the anode side. For comparison, a strip of filter paper from the same electrophoresis was fixed and stained for protein. Protein could be demonstrated in the region of the cathode vitamin B_{12}-binding peak, but not in the region of the anode peak. This did not necessarily mean that the vitamin B_{12}-binding compound on the anode side was not a protein, for protein may have been present in amounts too small to be demonstrated. If this were the case, the vitamin B_{12}-combining power of the compound per mg. would be very high—a possibility which we thought might indicate the presence of intrinsic factor.

This possibility was strengthened by the result of experiments in which extracts of pig's gastric mucosa (Ungley and Moffett, 1936) were subjected to ultrafiltration and electrophoresis. For when the source was fundus mucosa, which is clinically inactive, the anode peak was smaller—both relatively in comparison with the corresponding cathode peak, and absolutely, in terms of vitamin B_{12} bound per mg. of protein in the extract—than when the source was pylorus mucosa, which in the pig is a rich source of intrinsic factor (see Fig. 2).

The findings could also be expressed in terms of the amounts of material needed to ensure that 50 µg. vitamin B_{12} would be bound in the anode peak—namely, 500 ml. gastric juice, extract from 400 g. pylorus mucosa, and extract from 800 g. fundus mucosa. It was of interest to compare these amounts with doses used clinically—for example, a single dose of 500 ml. of gastric juice to potentiate 50 µg. vitamin B_{12} (Ungley, 1950) and daily doses of extract from 40 g. pylorus mucosa given with yeast extract

as extrinsic factor (Ungley and Moffett, 1936). The weaker binding activity of fundus mucosa was matched by its clinical inactivity in the dosage used.

These findings encouraged us to undertake electrophoresis on a larger scale, so that the fractions could be tested clinically. Some of this work was reported at the International Congress of Biochemistry in Paris in July, 1952,* when it was stated that material with intrinsic-factor activity had been separated from other vitamin B_{12}-binding substances in gastric juice. For at this time the selection of fractions was based on the distribution of peaks of vitamin B_{12}-binding activity. Subsequently, a method used for staining and scanning protein on filter paper after electrophoresis (Latner, 1952a, 1952b) was found to be equally effective.

In these earlier experiments vitamin B_{12} was added before electrophoresis, and barbitone buffer at *p*H 8.6 was used. Fractions from the cathode and anode vitamin B_{12}-binding peaks, tested in Cases 1 and 2, gave unsatisfactory results, which will not be described. About this time one of us (A. L. L.), in the course of collaborative work with Professor A. A. Harper in which paper electrophoresis was used, found that barbitone buffer at *p*H 8.6 could destroy the physiological activity of secretin. As it was thought that barbitone buffer might destroy intrinsic factor also, the following experiments were conducted with another buffer, the *p*H of which was 6.35.

MAIN OBSERVATIONS

Experiment A

The ultrafiltrate residuum from one litre of gastric juice was applied to paper strips and separated into 25 fractions by electrophoresis. The vitamin B_{12}-binding power of these fractions is shown in Fig. 3. Two or possibly three peaks were visible on the cathode side and four on the anode side of the line of application of the concentrate. As a first step towards determining where the intrinsic-factor activity lay, the 25 liquid fractions were separated into two groups. The group from the anode side was tested in Case 3, the cathode group in Case 4.

Case 3 (a Female Aged 62). Anode

In a preliminary period 50 μg. vitamin B_{12} administered orally alone produced merely a slight reticulocytosis of 4.2% without a rise in R.B.C. or P.C.V. When the same dose of vitamin B_{12} was given with the liquid fractions from the anode side, reticulocytes rose on the third day and reached a peak of 17.6% on the sixth day (Fig. 4). Clinical improvement was evident and R.B.C., Hb, and P.C.V. increased as follows:

Days:	0	5	10	15
R.B.C. (10^6 per c.mm.) ..	2·00	2·24	2·44	2·68
Hb (g. per 100 ml.) ..	9·3	10·1	10·5	10·5
P.C.V. %	21·5	24·0	27·0	29·0

Values continued to rise up to 81 days.

The increase of R.B.C. and P.C.V. in 15 days was slightly less than that which would be expected from an injection of 5 μg. (Ungley and Campbell, 1949, and unpublished). This result falls within the lower range of responses obtained with 50 μg. vitamin B_{12} and 500 ml. of gastric juice (Ungley, 1950).

Case 4 (a Female Aged 63). Cathode

The liquid fractions from the cathode side were administered orally together with 50 μg. vitamin B_{12}. There was no haemopoietic response. Subsequently a good response to the injected vitamin was obtained, but unfortunately the response to a potent oral preparation was never observed, so that the patient may have been resistant to oral therapy. Results reported later indicate that liquid from the cathode side usually does in fact possess some intrinsic factor activity. At this stage, however, we knew only that liquid from the anode side possessed such activity, whereas liquid from the cathode side might or might not be active. For this reason in the next three experiments, B, C, and D, only material from the anode half of the papers was tested clinically. In each instance material derived from 800 ml. of gastric juice was applied to six strips of paper.

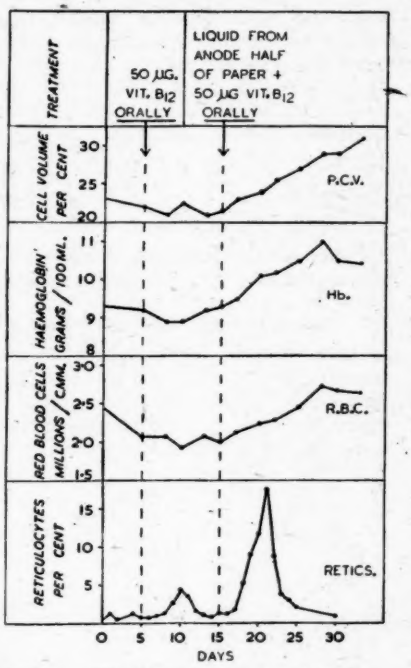

FIG. 4.—Clinical response to anode fractions in Case 3 (Experiment A).

Experiment B

Segments 1 cm. wide were drawn on the anode side of the line of application of material and numbered from 1 to 15. Liquid from segments 2, 3, and 4, which represented the B_{12}-binding peak on the anode side nearest to the starting position (see Fig. 5), was tested in Case 5.

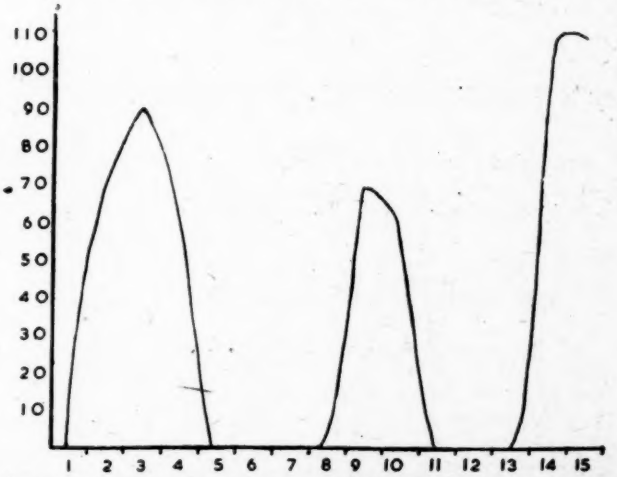

FIG. 5.—Vitamin B_{12}-binding in fractions obtained by electrophoresis of gastric juice used in Experiment B, in which only the anode side was tested.

Liquid fractions from the rest of the anode side were tested in Case 6. In this and subsequent experiments the anode and cathode peaks nearest to the line of application of concentrated gastric juice are referred to as the "first anode peak" and "first cathode peak" respectively.

Case 5 (a Female Aged 72). First Anode Peak

There was no reticulocyte response to 50 μg. vitamin B_{12} administered orally alone and the absolute values fell.

*Unfortunately, an account does not appear in the abstract, which was submitted long before the meeting.

When the same dose of vitamin B_{12} was given with the liquid from segments 2, 3, and 4, reticulocytes rose to a maximum of 10.3% on the sixth day. The R.B.C., Hb, and P.C.V. changed little :

	Days:	0	5	10	15
R.B.C.	.. .. ..	1·48	1·54	1·64	1·48
Hb	.. .. ..	6·2	6·2	7·3	6·5
P.C.V.	.. .. ..	15·0	16·5	19·0	17·5

There was subsequently a considerably greater response to a single oral dose of 3,000 μg. vitamin B_{12}.

Case 6 (a Male Aged 64). Rest of Anode Material

There was no response to 50 μg. vitamin B_{12} administered orally alone. An equal dose of the vitamin was then given together with the liquid from segment 1 and segments 5 to 15. Reticulocytes rose only to 2.8%, but there was some increase in absolute blood values.

	Days:	0	5	10	15
R.B.C.	.. .. ..	2·20	2·42	3·12	2·92
Hb	.. .. ..	10·4	11·3	12·1	11·4
P.C.V.	.. .. ..	31·0	35·0	37·0	35·0

Unfortunately, liquid from segment 1, which was erroneously included, might have had sufficient intrinsic factor activity to account for these changes. Desiccated stomach, 40 g. daily, subsequently produced a satisfactory increase in absolute values without a reticulocytosis.

Our conclusion from Experiment B was that the material corresponding to the first B_{12}-binding peak on the anode side had some intrinsic factor activity. The rest of the material from the anode side (which may have included part of the first peak) perhaps also had some intrinsic factor activity.

Experiment C

Fractions from this electrophoresis caused no response in Cases 7 and 8. Either the patients were resistant to oral therapy or any intrinsic factor present had been inactivated.

Experiment D

In this experiment a 1-cm. segment on the cathode side was included, together with the first four on the anode side, and tested in Case 9. Liquid from the rest of the anode side was tested in Case 10.

Case 9 (a Male Aged 38). First Anode Peak

There was no reticulocyte response to 50 μg. vitamin B_{12} administered orally alone, and absolute values fell slightly. When this amount of vitamin was given with the first anode peak (and one segment from the cathode side) reticulocytes rose to 8.6% on the fifth day. Absolute blood values (R.B.C., 1,200,000 ; Hb, 5 g.; P.C.V., 13.0%) showed little change. There was subsequently an excellent response to injected vitamin B_{12}.

Case 10 (a Female Aged 59). Rest of Anode Material

There was no response to 50 μg. vitamin B_{12} given orally alone. When 50 μg. was given with liquid from the rest of the anode side the response was negligible. There was no reticulocytosis, and the increase in absolute values was insignificant. The patient responded to desiccated stomach and later to injections of vitamin B_{12}.

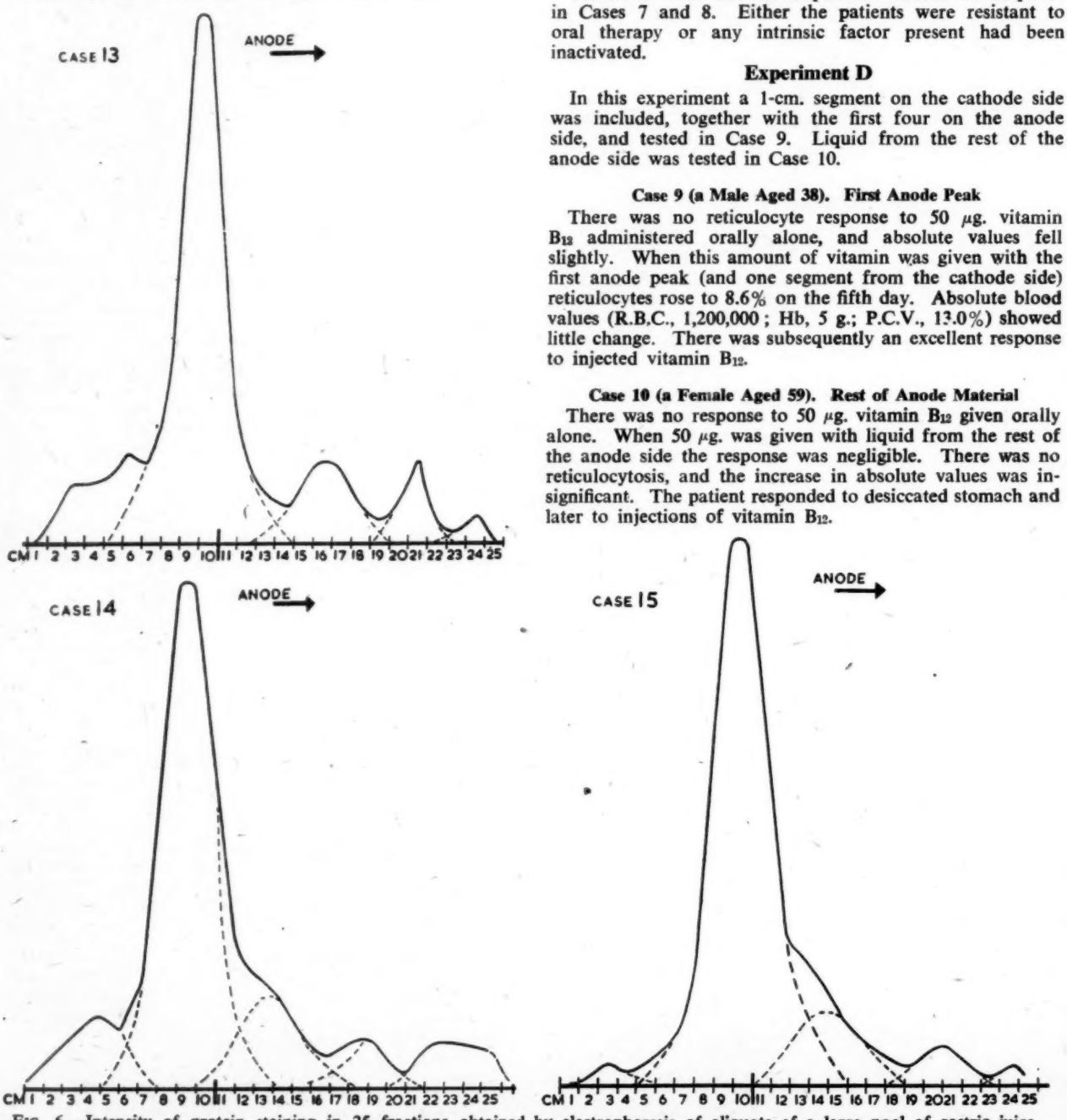

FIG. 6.—Intensity of protein staining in 25 fractions obtained by electrophoresis of aliquots of a large pool of gastric juice, and tested in Cases 13, 14, and 15 (Experiments F, G, and H).

Our conclusion from Experiment D is that any intrinsic-factor activity in the liquid from the anode side was mainly concentrated in the first anode peak, which in this case included one segment from the cathode side. There was little or no intrinsic-factor activity in the remainder of the anode side.

Experiment E

Neither of the patients (Cases 11 and 12) responded to the fractions administered. The same remarks apply as in Experiment C.

We now reached the conclusion that testing the various fractions from one electrophoresis in different patients was not completely satisfactory since individuals differ in their responses, especially to oral therapy. It was decided to test the fractions successively in the same patient, who then acted as his or her own control. We also reverted to our original procedure of testing fractions from both the anode and the cathode side of the starting position.

The three final experiments were carried out with a single pool of concentrated gastric juice. The aliquots taken for each electrophoresis corresponded to an original volume of 800 ml. The fractions after electrophoresis were tested not only for vitamin B_{12}-binding power but also for protein content. For the latter purpose 0.02-ml. portions of each fraction were placed in line on a strip of filter paper. The spots were fixed in the oven and stained by a technique already described (Latner, 1952a). The stain used, naphthalene blaek, is not necessarily specific for protein. The density of each stained spot was determined with a modified Spekker absorptiometer (Latner, 1952b), and plotted graphically as shown in Fig. 6. The peaks so obtained agreed fairly closely with the peaks of vitamin B_{12}-binding obtained microbiologically. Since the staining method was less arduous and gave smooth, easily reproducible curves, it was used henceforth as the guide for grouping fractions for clinical trial.

Experiment F

Several peaks were demonstrated by the staining method (Fig. 6, Case 13). The material was subdivided into three groups of fractions corresponding to the first anode peak, the first cathode peak, and the rest of the material. These were tested in successive periods in Case 13. Disappointingly, there was no response to any of them. A review of the technique suggested that there may have been undue warming during manipulation. In subsequent experiments, therefore, special care was taken to keep the material cool at all stages and in particular during centrifuging.

Experiment G

The peaks demonstrated by staining are shown in Fig. 6, Case 14. This material was also subdivided into three groups of fractions and tested in successive periods in Case 14 (see Fig. 7).

Case 14 (a Male Aged 60)

In the first period 50 μg. vitamin B_{12} was given with liquid from segments 1 to 6 and 18 to 25. There was no response. In the second period the same amount of the vitamin was given with liquid from segments 7 to 10 (the first cathode peak). Reticulocytes rose to 15% on the fifth day and absolute blood values increased.

	Days:	0	5	10	15
R.B.C.	.. .. ..	1·52	1·60	2·12	2·02
Hb	.. ..	5·9	6·4	7·8	7·7
P.C.V.	.. .. ..	15·0	18·2	24·6	24·2

In the third period, when liquid from segments 11 to 17 (first anode peak) was given with 50 μg. vitamin B_{12}, there was a further reticulocytosis of 8.6% on the seventh day. Because of the higher initial R.B.C. level, this reticulocytosis is as significant as the peak of 15% in the preceding period. For similar reasons the increases in absolute blood values were also more significant.

	Days:	0	5	10	15
R.B.C.	.. .. ..	1·94	2·00	2·92	2·96
Hb	.. .. ..	7·4	7·8	10·1	10·4
P.C.V.	.. .. ..	23·5	25·5	34·0	32·5

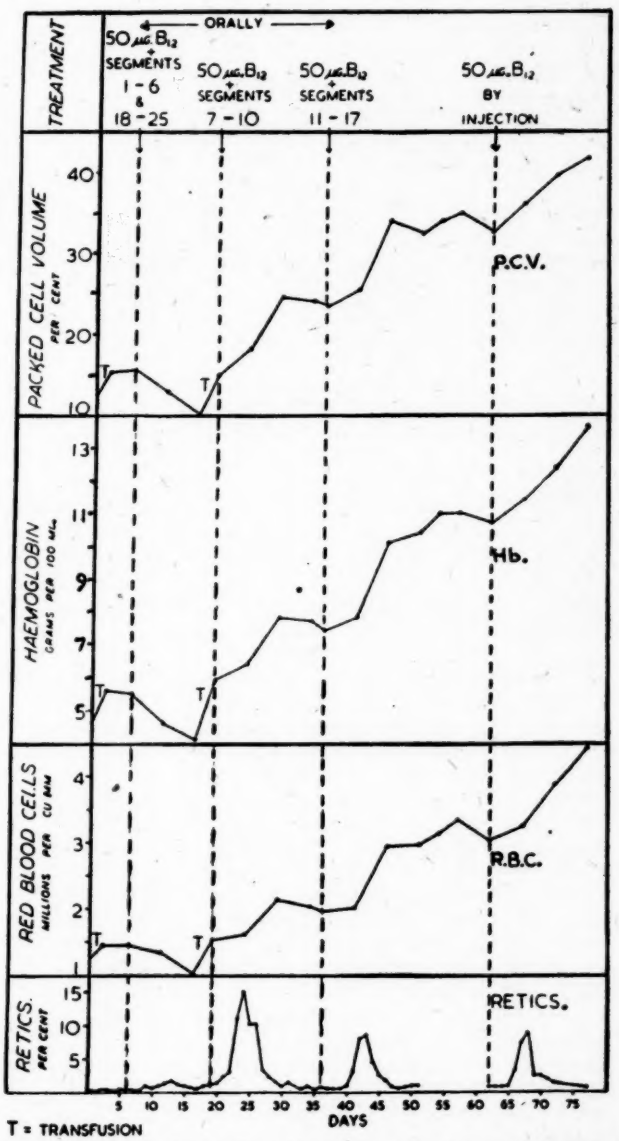

FIG. 7.—Clinical trials in Case 14; responses to first cathode peak (segments 7–10) and first anode peak (segments 11–17), but no response to rest of material (segments 1–6 and 18–25).

The increases of P.C.V. and R.B.C. in the second period were much less than would be expected from an injection of 5 μg. vitamin B_{12}. In the third period the increases were equivalent to those which would be expected from an injection of 5–10 μg.

Our conclusion from Experiment G is that the material corresponding to the first anode peak had a substantial amount of intrinsic-factor activity. It was particularly rich in terms of activity per mg. of stained material. Some intrinsic-factor activity stayed with the first cathode peak, but the activity of this region per mg. was much less than that of the first anode peak.

Experiment H

This experiment was similar to the previous one. The peaks demonstrated by staining are shown in Fig. 6, Case 15. The various fractions were tested in Case 15.

Case 15 (a Female Aged 56)

In the first period 50 μg. vitamin B_{12} was given with liquid from the outer segments of cathode and anode sides (segments 1–6, 18–25). Reticulocytes rose only to 4.4% on the sixth day, and absolute blood values remained unchanged.

In the next period 50 μg. vitamin B_{12} was given with the liquid corresponding to the first cathode peak (segments 7–10). Again reticulocytes rose to only 4.2% on the sixth day, although this time there was a very slight increase in absolute values.

Days:	0	5	10	15
R.B.C.	1·76	1·68	2·16	2·16
Hb	7·8	7·8	8·7	8·4
P.C.V.	22·0	22·0	26·0	26·0

In the third period 50 μg. B_{12} was given with the material corresponding to the first anode peak (segments 11–17). Reticulocytes rose to 7.2% on the sixth day, and the increase in absolute values was more significant.

Days:	0	5	10	15
R.B.C.	2·40	2·81	3·08	2·88
Hb	9·6	10·8	11·1	10·8
P.C.V.	25·7	31·0	31·0	29·0

The same conclusions were drawn from this experiment as from Experiment G. The liquid corresponding to the first anode peak was the richest in intrinsic factor, especially in terms of activity per mg. of stained material. Some activity stayed with the liquid corresponding to the first cathode peak.

Discussion

It has thus proved possible to fractionate intrinsic-factor activity in human gastric juice by preparative paper electrophoresis. Vitamin B_{12}-binding and later a method of protein staining were used as aids to the grouping of fractions for clinical trial.

When highly concentrated gastric juice was used, a "protein" peak could be detected in association with every vitamin B_{12}-binding peak. This suggests that our inability to demonstrate such a peak corresponding to the anode vitamin B_{12}-binding peak in an earlier experiment (see preliminary observations) was probably due to insufficient concentration of the gastric juice. It will be remembered that in this experiment the juice was concentrated only 20 times.

In experiment A, intrinsic-factor activity was clearly demonstrated in the anode fractions. But the absence of response to the cathode fractions did not necessarily mean absence of intrinsic-factor activity, for the recipient (Case 4) may have belonged to a group of patients who respond poorly to orally administered material. Of 10 patients with pernicious anaemia to whom 50–80 μg. vitamin B_{12} was administered with 500 ml. gastric juice, no fewer than three had very trivial responses, and one failed to respond (Ungley, 1950, and unpublished).

It is interesting to note that in the last two experiments, G and H, when larger quantities of gastric juice were used, tests showed the presence of some intrinsic factor in material corresponding to the first cathode peak as well as to the first anode peak. The reaction to the anode peak material seems to be the more significant, for its activity is as great as or greater than that of the cathode peak material although the former contains much less protein.

In view of our finding that intrinsic-factor activity is associated with material corresponding to two peaks, it is interesting to speculate that the substance may exist in gastric juice both in a free and in a combined state. The former might be represented by the first anode peak and the latter by the first cathode peak. We already have evidence that the material of the first anode peak contains either a mucoprotein or a mucopolysaccharide, and that heparin, a related substance, has significant vitamin B_{12}-binding power. These facts will be reported in greater detail elsewhere. We have also shown that the material of the first cathode peak, although it contains much more mucoprotein, has less intrinsic-factor activity. This may well represent the fraction isolated by Glass *et al.* (1952). It is possible, however, that the activity of the cathode peak material may have been due not to a chemical combination but to overlap of the peaks or to some physico-chemical phenomenon associated with the electrophoresis on filter paper of concentrated and highly viscous solutions.

In Experiments G and H the weight of organic material from the first anode peak was of the order of 40 mg. It would be misleading to compare this quantity with the daily dose of 0.6 mg. with which Welch and Heinle (1951) produced a response in one case. Our method has been to give a single dose orally and to evaluate the result on the rate of increase of R.B.C. and P.C.V. in 15 days (Ungley, 1950). Reticulocyte responses may provide evidence of the presence or absence of activity, but they are not a satisfactory basis for quantitative assessment (Ungley and Campbell, 1949). As determined by reticulocyte response, even 10 ml. of gastric juice daily was enough detectably to potentiate an oral dose of 5 μg. vitamin B_{12} (Schilling *et al.*, 1950; and Castle, 1951, personal communication). Until details of their case are published it cannot be assumed that the 0.6 mg. of material used by Welch and Heinle (1951) had any greater activity than 10 ml. of gastric juice.

In Experiments G and H our material produced not only a reticulocytosis but a significant increase of R.B.C. and P.C.V. within the range of responses we have obtained with a single dose of 500 ml. gastric juice and 50 μg. vitamin B_{12} (Ungley, 1950, and unpublished). The magnitude of these responses makes it reasonably certain that appreciably smaller doses, perhaps differing little from those used by Welch and Heinle in the single case referred to above, might have sufficed to produce a reticulocytosis alone.

But, whatever the basis of haematological assessment, allowance must be made for the wide scatter in the responses of different patients to equal dosage. This scatter is wide even when vitamin B_{12} is administered parenterally, especially if the dose is less than 10 μg. (Ungley and Campbell, 1949, and unpublished). The scatter is even wider when the vitamin is administered orally, for increases of R.B.C. and P.C.V. tend to be small and individual differences in absorption are great. When different observers are concerned there are certain also to be differences in strictness of control, limitation of diet, and so on. Because of all these variables, attempts to compare the activity of our material with that of others might involve errors of several hundreds per cent.

Even an approximate comparison would call for many more clinical trials—preferably trials in each of which the two materials would be tested serially in one patient, as in our Experiments G and H. Alternatively, activities could be compared by the technique of Welch, Scharf, Heinle, and Meacham (unpublished data cited by Welch and Nichol, 1952). These authors measured the radioactivity of the stools of patients with pernicious anaemia in remission after administration of radioactive vitamin B_{12}, at first alone and then together with a source of intrinsic factor.

Welch and Nichol (1952) remark that a daily dose of 3 mg. of a crude concentrate of hog's stomach will promote the absorption of 0.5 μg. radioactive vitamin B_{12}. It is possible, however, that 10 times this daily dose of their intrinsic factor concentrate might be needed to potentiate 5 μg. vitamin B_{12} administered orally to patients with pernicious anaemia in relapse.

Summary

Concentrated human gastric juice was subjected to preparative electrophoresis on filter paper. Several peaks were demonstrated by a protein-staining method. All had vitamin B_{12}-binding activity. Material from two of them—one on the cathode side and one on the anode side of the starting-point—was shown clinically to possess intrinsic-factor activity. Material correspond-

ing to the anode peak, which appeared to be the more active of the two, has been shown to contain either a mucoprotein or a mucopolysaccharide.

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THE DEFINITION AND ASSESSMENT OF RESPIRATORY FUNCTION*

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PART II

FACTORS AFFECTING THE TRANSFER OF OXYGEN IN THE LUNGS

It has already been emphasized that the main function of the lungs is the transfer of adequate quantities of oxygen to the blood to maintain a normal oxygen tension and content in the blood flowing to the body, no matter what the degree of activity or how great the oxygen utilization of the tissues. The removal of excess carbon dioxide from the blood rarely presents any difficulty in disease, except in a few special circumstances. I will therefore confine my main discussion to the problem of oxygen transfer.

Distribution of Blood and Gas to the Alveoli

The alveolus is the unit of lung anatomy and lung function. All aspects of structure and function are subservient to the proper supply of each alveolus with blood and gas in correct quantities so that an adequate oxygen tension gradient and gas transfer between them is maintained. In a theoretically perfect lung the inspired air that passes the anatomical dead space would be equally divided among all alveoli. In other words, if there were, for argument's sake, one million alveoli, then each would receive one-millionth of the effective inspired air that enters the alveoli. Similarly in such a lung each alveolus would receive one-millionth of the cardiac output. Such a state of affairs would represent perfect blood and gas distribution and each of the million alveoli would have the same ratio of ventilation and perfusion as all the other alveoli and the total lung itself. The resultant gas and blood tensions in each alveolus would be similar to all other alveoli, and each will be a miniature lung in all respects.

It is easy to imagine various disturbances of blood and gas distribution that could occur. Certain alveoli could receive less than their "share" of ventilation and yet be perfused with their normal "quota" of mixed venous blood. The blood leaving such alveoli and joining the left heart outflow would be inadequately oxygenated.

Next there could be imperfect distribution of blood; this would result in alveoli which are adequately ventilated no longer receiving their quota of mixed venous blood from the right heart. Such blood-distribution defects would not cause any deficiency of blood oxygenation but would manifest themselves in the expired air, which would contain a larger-than-normal percentage of unchanged inspired air.

We shall see later how near normal and diseased lungs come to these entirely theoretical concepts of perfection and imperfection of blood and gas distribution.

Oxygen Transfer (Diffusion) in the Lungs

The diffusion characteristics of a membrane, in regard to a particular gas such as oxygen, can be described by the quantity of oxygen that passes across it in unit time when there is a unit pressure gradient of oxygen across the membrane. This quantity of gas, or the diffusion coefficient, will depend on a number of fairly obvious factors—surface area, thickness, and physical characteristics. If we wish to consider the diffusion characteristics and coefficient of the pulmonary membrane, we must remember that we are dealing with a very complicated structure. It will include all the tissues and fluids between alveolar gas and the haemoglobin molecule in the red blood cells in the pulmonary capillary. It is also possible that the effective area of this "membrane" may vary greatly in the normal lung during various degrees of activity. Marie Krogh (1915) attempted to measure the oxygen diffusion coefficient of the lungs in normal subjects by the use of carbon monoxide. This gas was used because it is taken up by haemoglobin with such avidity that its tension in the pulmonary capillary blood (amount in simple solution) was assumed to be zero at all times. The diffusion coefficient of oxygen was easily determined from these data, as the coefficient of each gas is a simple function of its solubility and molecular weight.

Since that time little definitive work has been done on this subject, but attempts have recently been made to measure the diffusion coefficient of oxygen more directly during normal respiration (Lilienthal *et al.*, 1946). This presents great difficulty even in the normal lung, where it can be reasonably assumed that the alveolar oxygen tension is fairly constant through all alveoli. If the alveolar oxygen tension is known, then the initial pressure gradient between this and the mixed venous blood entering the alveoli can be determined by cardiac catheterization. However, the determination of the final and mean gradient between the alveolus and capillary blood presents more difficulty. These difficulties are even greater in subjects with lung disease, in whom the alveolar oxygen tension may also vary greatly. The diffusion coefficient cannot be measured unless the mean alveolar capillary oxygen tension gradient is known.

Alveolar Gas Tensions. The Concept of Ideal Alveolar Gas Tensions

The determination of the actual gas tensions in the alveoli during normal respiration presents great difficulties. Without this information the analysis of blood and gas distribution and gas transfer would seem impossible. The Haldane (1915) technique of making a subject expire deeply and collecting the sample at the end of expiration has long been used for this purpose. There is no certainty that the gas obtained in this way is an accurate, statistically repre-

*Adapted from the lectures given in the "Science and Medicine" series, Postgraduate Federation (London University), 1950–1. Part I was published in last week's issue, p. 415.

sentative sample of the gases actually present in the alveoli. Further, this method of sampling interrupts the normal rhythm of respiration and alters the very values it is attempting to determine. Various devices for aspirating a small quantity of gas from the end of each normal expiration over a period have been used; this avoids upsetting the natural respiration and gives far more repeatable results in normal subjects (Rahn *et al.*, 1946). However, the underventilated alveoli will not be adequately represented in such a sample. Recently new concepts and methods have partially solved these difficulties. Fenn *et al.* (1946) pointed out that, in the steady state, the difference of pressure of oxygen and carbon dioxide in the alveoli and the inspired air was a measure of the quantities of these gases being absorbed and excreted by the lungs. Now these quantities of gases are related, their ratio being the respiratory quotient, which is easily determined by the analysis of expired air collected over a period thus:

$$\text{Respiratory quotient} = \frac{CO_2 \text{ excreted}}{O_2 \text{ absorbed}} = \frac{\text{Pressure gradient of } CO_2 \text{ between alveoli and inspired air}}{\text{Pressure gradient of } O_2 \text{ between alveoli and inspired air}}$$

As the pressure of CO_2 in the inspired air is negligible the equation becomes:

$$R.Q. = \frac{\text{Alveolar } pCO_2}{\text{Insp. } pO_2{}^* - \text{alv. } pO_2}$$

$$\text{or Alv. } pO_2 = \text{Insp. } pO_2{}^* - \frac{\text{alv. } pCO_2}{R.Q.}$$

It will be obvious that to define the alveolar gas in a single equation, in which the body R.Q. describing total gas exchange is employed, is to assume that all alveoli are equally ventilated and perfused and have the same R.Q. and gas tensions. It would seem that this equation gives little advantage, as the alveolar pCO_2 is now needed to determine the alveolar pO_2.

Riley *et al.* (1946) pointed out that the arterial pCO_2 could be regarded as accurately representing the alveolar tension of carbon dioxide (pCO_2), as, owing to the extremely high rate of diffusion of carbon dioxide in fluids, there must be almost absolute equilibrium of this gas between alveolar gas and blood leaving the alveoli. Again, this would be valid only if the distribution of the blood and gas were perfect. Yet Riley and Cournand (1949, 1951) pointed out that even if there is considerable underventilation of normally perfused alveoli (poor gas distribution) the arterial pCO_2 will differ but little from that which would obtain in a perfect lung with perfect blood and gas distribution. The reason for this superficially surprising fact is that there is only 4–5 mm. difference in the pCO_2 of normally ventilated and of unchanged mixed venous blood, owing to the enormous capacity of the blood for this gas. Thus in most patients with diseased lungs the increase of the arterial pCO_2 above what would be found in the same patient with ideal lungs and perfect gas and blood distribution is rarely significant. This is a most important observation and the key to many advances. It means that the "alveolar oxygen tension" as calculated from the inspired oxygen tension and the arterial pCO_2 and body R.Q. is, even in abnormal subjects, very close to what the alveolar tension would be if the lungs were "ideal" and had perfect distribution of blood and gas and all alveoli had similar gas tensions. It is therefore an easily obtained arbitrary measure of perfection, and the deviation of gas and blood coming from the lungs from this theoretical figure gives much information concerning any departure from complete homogeneity of the ventilation–perfusion relationships of the alveoli.

Venous Admixture Effect

The effect of underventilation of alveoli on the arterial oxygen tension is considerable, as the difference in oxygen tension between mixed venous blood and adequately ventilated blood is of the order of 60 mm. Hg. Riley and Cournand (1949) therefore attempted to assess the underventilation of alveoli in the following manner. They studied a normal subject in the steady state and determined the inspired air oxygen tension, the body R.Q., and the arterial pCO_2. From these data they could calculate by the above equation the only alveolar oxygen tension that was possible if all alveoli were homogeneously ventilated and perfused. They then calculated what the percentage oxygen saturation of arterial blood would be if it had all passed through homogeneous "ideal" alveoli. For good reasons, which will be discussed later, they assumed that there was virtual equilibrium of oxygen tension between alveolus and blood in normal subjects when breathing air.

They then compared this arterial percentage oxygen saturation with that actually found in the subject. Any passage of blood through underventilated alveoli or systems unrelated to air spaces would cause the arterial saturation to be lower than the calculated ideal figure. They then expressed the drop of percentage oxygen saturation from the ideal as a certain percentage of unaltered mixed venous blood being added to ideally ventilated blood. This figure, stated as *percentage venous admixture*, is a measure of perfusion of poorly ventilated alveoli or of direct venous addition (bronchial veins, thebesian veins, etc.) to the blood in the left heart. It is in fact an integration of all degrees of imperfection of ventilation of blood passing through the lungs into ideal ventilation and complete lack of ventilation. In normal subjects studied the arterial oxygen tension is only a few millimetres below the "ideal" figure and the percentage venous admixture is usually well below 5%, over 95% of the cardiac output being perfectly oxygenated. This emphasizes how remarkably near to perfection the distribution of blood and gas is in the normal lung. It is not yet known whether the "venous admixture" is due to anatomical venous admixture, to a slight degree of alveolar underventilation, or to a combination of the two.

Dead-space Effect

Just as poor gas distribution, or alveolar underventilation, is studied by its effect on the arterial blood, so inefficient blood distribution, or alveolar underperfusion, can be assessed by the analysis of expired air. It is now well established that in a normal person two-thirds or more of the tidal air passes the conducting air passages in which significant gas exchange does not occur and enters the alveoli. As all the gas leaving the alveoli has been in virtual carbon dioxide equilibrium with the blood leaving the alveoli, then this gas will have a similar carbon dioxide tension to the arterial blood. In an ideal lung, which the normal closely approaches, all alveoli will be equally ventilated and perfused and thus the expired gas will have a carbon dioxide tension which is at least two-thirds of the arterial carbon dioxide tension, as two-thirds will be from the alveoli and not more than one-third returned unchanged from the anatomical dead space. The small amount of air leaving poorly ventilated alveoli will, for reasons already given, have a pCO_2 very close to the arterial pCO_2 and have little effect on the expired pCO_2. However, if there is poor distribution of blood to alveoli and a number are well ventilated but not perfused with venous blood, then the gas leaving these alveoli will be unchanged inspired air. Similarly, if the blood perfusing ventilated alveoli is reduced then less oxygen will be extracted and less carbon dioxide will be added to the alveolar gas. This will result in the gas leaving the alveolus being nearer in composition to inspired air than that from normally ventilated and perfused alveoli.

Now, many studies in various lung diseases have shown no significant increase of the anatomical dead space. Thus if the pCO_2 of the expired air is less than two-thirds of the arterial pCO_2 then this is regarded as good evidence of the ventilation of unperfused and poorly perfused alveoli. The overventilation of normally perfused alveoli will also add to this so-called "dead-space effect." This is an extension of Bohr's concept of the physiological dead space, which

*Corrected for change in volume as in oxygen-consumption determination from analysis of expired air.

again integrates the various degrees of imperfection of distribution into absolute lack of alveolar perfusion and ideal ventilation and perfusion. The dead-space effect can be stated as a percentage of tidal air or of total ventilation. It is estimated as follows:

$$\text{Dead-space effect (as \% tidal air or total ventilation)} = \frac{\text{Arterial } pCO_2 - \text{Expired } pCO_2}{\text{Arterial } pCO_2} \times 100$$

Diffusion Gradients in the Alveolus

It will be remembered that so far in this discussion it has been assumed that when a normal subject breathes air the transfer of oxygen across the pulmonary membrane is so efficient that there is no appreciable oxygen tension gradient between the alveolar gas and the blood leaving the alveolus, and that the diffusion factor did not contribute in the normal subject to the slight depression of arterial oxygen tension below the theoretical ideal. Let us return to the question of whether it is reasonable to assume that this depression of the arterial oxygen tension is due only to so-called "venous admixture" or distribution disturbance.

Lilienthal *et al.* (1946) studied the alveolo-arterial oxygen tension gradient in normal subjects breathing low percentages of oxygen. Under these conditions the effect of alveolar under-ventilation becomes insignificant and the whole of the alveolo-arterial oxygen tension gradient can be safely assumed to be due to the final alveolo-capillary gradient in the alveoli (final diffusion gradient). This allowed the mean oxygen tension gradient between the alveolus and capillary to be calculated, and from this the diffusion gradient (O_2 uptake per minute mean diffusion gradient). By applying this diffusion coefficient to the data obtained while the subjects were breathing air, they showed that under these conditions the mixed venous blood reaches oxygen tension equilibrium with the alveolar gas when it is about halfway through the alveolar capillary. They were thus able to state that the slight alveolo-arterial oxygen tension gradient in normal subjects when breathing air was due to slight distribution disturbances—that is, venous admixture.

The application of this "two-level" technique to abnormal patients presented many great difficulties. A smaller degree of anoxia was advisable, and it could not be assumed that distribution or diffusion gradients were negligible at any particular level of oxygen breathing. These difficulties were overcome (Riley *et al.*, 1951), and the resultant studies (Donald *et al.*, 1952) have allowed the disturbances of blood and gas distribution and of alveolo-capillary oxygen diffusion, and their role in arterial desaturation, to be more precisely assessed in various lung diseases. The most important findings can be briefly outlined.

Two main groups of patients were studied by this technique. Those in the first group were suffering from pulmonary disease in which the pathological processes involved the alveolar walls and in which interference with the diffusion of oxygen across the pulmonary membrane was suspected (Baldwin *et al.*, 1949a). The second group consisted of patients with pulmonary emphysema in whom impairment of the efficient distribution of blood and gas to the alveoli was thought to be the main disability.

Pulmonary "Infiltration," or "Pneumonitis"

These patients complain of severe shortness of breath on very slight exertion. All show radiological evidence of widespread pulmonary infiltration. Although the physiological findings are remarkably constant, there is a very wide range of diagnoses. These include beryllium granuloma, asbestosis, scleroderma, Boeck's sarcoid, reticuloses, "interstitial pneumonitis," and various unclassified granulomata. In those patients coming to necropsy the occurrence of pathological tissue in the alveolar walls can be demonstrated. All the patients studied had no spirometric evidence of ventilatory obstruction, and the residual volumes were equal to or less than the predicted normal range. The normal or nearly normal ventilatory capacity (M.B.C.) in all cases was further evidence that emphysema was not present. At rest the arterial blood saturation was normal or only very slightly depressed, whereas on very mild exercise marked arterial blood desaturation associated with considerable dyspnoea occurred, despite the unimpaired ventilatory capacity.

In some of these patients, studied at rest, the gas and blood distribution in the lungs was normal, as shown by the normal dead space (33%) and the normal venous admixture effect (6%). Yet the mean oxygen diffusion gradient (mean alveolo-capillary oxygen tension gradient) was about twice that found in normal subjects (normal, 20 mm. Hg), the diffusion coefficient being abnormally low (normal, 15 ml./mm./minute). Thus the interference with the transfer of oxygen across the alveolar membrane, despite the relatively efficient distribution of blood and gas to the alveoli, which had been previously suspected in these cases, was now definitely demonstrated. This interference with the oxygen diffusion necessitated an increased oxygen tension gradient between alveolus and capillary to maintain the transfer of even the resting oxygen requirements.

Let us contrast these patients with normal subjects. It has been pointed out already that, under resting conditions, the blood in the normal alveolar capillary reaches almost complete oxygen equilibrium with the alveolar gas in just over half the capillary length. Further, when a normal subject exercises there is probably a considerable increase in the diffusing capacity of the lung due to this expansion of the alveolar capillaries or the opening up of new capillaries. Even if this mechanism is greatly limited the "reserve" distal half of the lung capillaries will allow a large increase in capillary blood velocity, even with the same or increased mixed venous blood desaturation, without any risk of incomplete oxygenation of the blood leaving the alveolus.

In this group of patients a measurable oxygen tension gradient between the alveolar gas and the blood leaving the alveolus could be demonstrated when air was breathed in the resting state. Thus the normal reserve of lung capillary was no longer available. It is probable that the ability to expand the pulmonary capillary bed and increase the diffusing capacity was also much impaired. More important is the fact that any increase in the velocity of blood through the lung capillary will inevitably increase the final alveolo-capillary oxygen tension gradient, and thus the blood leaving the lungs and entering the systemic circulation will be considerably desaturated. In more simple terms these patients show marked cyanosis and distress on exercise because they have no reserve diffusing capacity.

In the more severely affected patients not only was the diffusion of oxygen even more impaired but the dead-space and venous admixture effects were greatly increased. It was considered, in the absence of emphysema, that this was probably due to such severe involvement of the alveolar membrane in certain portions of lung that no significant gas exchange was possible, and that gas and blood were returned unchanged from such areas.

Pulmonary Emphysema

The patients investigated all had clinical and radiological evidence of emphysema. Lung-volume studies showed the usual increase of residual volume and decrease of maximum breathing capacity. A number of these patients showed moderate arterial blood desaturation at rest and considerable desaturation on exercise. Raised arterial blood carbon dioxide tensions were found in some cases.

It has been demonstrated in many ways that the distribution of inspired air throughout the lungs is exceedingly uneven and inefficient in this disease. The uniform distribution of blood is probably also impaired in emphysema owing to the damage to the finer branches of the pulmonary vascular tree; but there is so far only indirect evidence of this, such as histological and injection studies, and haemodynamic studies of the pulmonary circulation during rest and exercise.

In this investigation considerable increase of the dead-space effect (ventilation of underperfused and unperfused alveoli) and of venous admixture effect (perfusion of underventilated or unventilated alveoli) was demonstrated. In some patients the dead-space effect was well over 60% of the tidal air, the upper limit of normal dead space due to the conducting passages being about 33% of the tidal air. Similarly, venous admixture effects of nearly 50% of the cardiac output were found. Such findings indicated gross upset of the normal distribution of blood and gas to the alveoli and of the efficient correlation of alveolar ventilation and circulation. It must be remembered that, as it is impossible to describe the almost infinite variations of ventilation–perfusion relationships, the present method integrates all departures from homogeneity into ideal ventilation–perfusion relationship and into the return of unchanged gas and blood from the lungs.

It was also found that an increase of dead-space effect was not always associated with a similar increase of the venous admixture effect, and vice versa. This is an important finding, as it means that emphysema may interfere predominantly with alveolar ventilation in certain cases and with alveolar circulation in others. It may also explain the remarkable variation in disability and prognosis in this disease.

A somewhat unexpected finding in a number of these patients was a greatly increased oxygen diffusion gradient (mean alveolo-capillary oxygen tension gradient) and a decreased diffusion coefficient. Histological studies in emphysema do not suggest any structural interference with the diffusion of oxygen across the alveolar membrane. However, it must be remembered that lung which is ventilated but not perfused, or perfused but not ventilated, is as functionless as lung that receives neither blood nor air. Thus these distribution disturbances will render large amounts of lung quite functionless, and the effective blood–gas interface where blood and gas meet and there is an adequate gas gradient between them will become less and less as these disturbances increase.

In confirmation of this, the most pronounced impairment of diffusing capacity was found in those patients with the largest combined venous admixture and dead-space effects. Just as the area of the pulmonary membrane and the diffusing capacity will become less and less in patients whose lungs are being progressively destroyed by infection or cystic disease, so increasing disturbances of alveolar ventilation and perfusion will also reduce the amount of effective lung and diffusing capacity.

The findings further suggested that deficient arterial blood oxygenation at rest in emphysema is mainly due to alveolar underventilation, whereas marked arterial desaturation on exercise, as in the previous group described, was due to the limited diffusing capacity of the lung.

Practical Considerations

The methods required in such studies need a large trained team and generous facilities. These studies are necessary for furthering our knowledge of lung function but are quite impracticable as routine investigations. However, without such experiments the value and significance of the more simple tests which can be used in clinical medicine will remain obscure.

Arterial Blood Studies

In routine clinical work the commonest cause of severe cyanosis is severe congestive cardiac failure due to rheumatic heart disease. These patients have greatly reduced cardiac outputs, and their cyanosis is caused by the inevitable extraction by the body tissues of an unusually large percentage of oxygen from the reduced amount of circulating blood. Yet they have normal or nearly normal arterial blood oxygenation. Again, many patients with congenital heart disease and arterial blood desaturation have considerable polycythaemia, and their cyanosis is further increased because of this.

In most patients with lung disease the cardiac output is normal and marked polycythaemia is not present. In such patients it is most difficult to assess the degree of arterial blood oxygenation by visual inspection, and they may be dangerously anoxaemic with only what seems to be very slight cyanosis. Although the difference between "peripheral" and "central" cyanosis has been long appreciated, the difficulty of assessing the latter, particularly if acute, and its sinister import if marked, is not so clearly understood. In all cases of respiratory disease, whether acute or chronic (apart from pneumonia responding rapidly to treatment), the determination of the arterial blood oxygenation is as essential and obvious an investigation as the determination of the blood urea in kidney disease.

With practice arterial puncture is a smooth, easy, and painless procedure. The brachial artery is almost always used in respiratory studies, as most patients are conditioned to assault in this region and are not disturbed. It is not justifiable to risk damaging the femoral artery in middle-aged and elderly patients, as the circulation is always more precarious in the leg than in the arm. Further, the patient can be exercised without disturbing the needle. The best needle for this type of work is the Riley modification of the Cournand indwelling arterial needle, although, if only a single sample is needed, any medium-sized needle can be used, providing the bevel is kept short. The arterial blood is collected into a heparinized syringe and sealed after a drop of mercury has been added to facilitate mixing. It is quite incomprehensible why a number of workers continue to transfer these beautifully sealed blood samples to another vessel under oil. It is not only messy but an unnecessary additional manipulation. Further, the carbon dioxide diffuses through the oil at a high rate and is lost to the atmosphere. There is therefore a variable loss of this gas and change in the *p*H of the blood. Even more serious is the fact that when the sample is left to stand sedimentation of red cells occurs. Most vigorous stirring under oil will not give homogeneous red cell distribution, and thus samples taken for analysis may vary considerably and contain a greater concentration of red cells than in the original sample (Donald and Wade, 1952). A sealed syringe can be placed on a conical roller and the blood will remain well mixed until the analysis.

The most accurate method of determining the oxygen and carbon dioxide content of blood is the Van Slyke and Neil manometric technique (Peters and Van Slyke, 1932). The Haldane blood–gas analysis method is also satisfactory for determining the oxygen content if the Courtice and Douglas (1947) modifications are used. It takes less time than the Van Slyke method. However, the reliability of all methods is checked against Van Slyke determinations, and if several of these instruments are used, and all concerned are trained in its use, then the more reliable and accurate method can be employed without undue loss of time. An important point is that the oxygen capacity of arterial blood varies in different states and exercise will cause it to rise considerably. The use of a resting capacity in exercise studies may cause considerable errors.

If more precise and fundamental work is being done then it is necessary to measure the arterial blood–gas tensions. This procedure, although not yet suitable for routine clinical studies, is essential in the study of blood oxygenation in lung diseases. A glance at the oxyhaemoglobin dissociation curve will show why tension studies are so necessary for more precise work. It will be seen that, provided the blood *p*H does not alter, a fall in blood oxygen tension from 100 to 62 mm. Hg involves a drop of haemoglobin saturation of only 97 to 90%. Thus disturbances in alveolar ventilation or oxygen transfer have to be quite gross before pronounced arterial blood desaturation is obtained.

The bubble equilibration method of Riley, Proemmel, and Franke (1945), although not perfect and demanding great skill, is an essential weapon in modern respiratory research. Without it, as already emphasized, only the most severe disturbances in blood oxygenation can be demonstrated. It is unwise to attempt to develop this technique without first seeing it done by a worker who is trained in the method.

When arterial blood is being taken for gas-tension studies it is necessary to collect the expired air at the same time,

so that the expired-gas tension and respiratory quotient can be determined. This allows the ideal alveolar oxygen tension to be calculated and thus the gradient between this and the arterial oxygen tension. This is the most accurate and delicate method of expressing how far arterial blood oxygenation falls short of perfection.

Finally, let us consider the value of studying the oxygen and carbon dioxide content of arterial blood in various lung diseases.

Resting Studies

The arterial blood desaturation in emphysematous subjects at rest is never of the extreme order seen in many cases of congenital heart disease, unless there is extreme interference with alveolar ventilation due to acute bronchitis, severe asthma, or pneumonia. Figures below 85% saturation are unusual, but even this is roughly equivalent to 40% of the blood from the right heart passing through the lungs unchanged. This would again emphasize how relatively insensitive arterial blood saturation is as a measure of defective alveolar ventilation. It may also explain why marked polycythaemia is not often encountered in this disease. In fibrosis and pathological infiltrations of the lung there is rarely any significant arterial desaturation at rest.

Speaking in general terms, the arterial desaturation at rest is due to the venous admixture effect from underventilated alveoli and is not caused by any limitation of the diffusing capacity, which is adequate in the resting state even in patients with severe diffusion disturbances.

Patients may suffer severe anoxaemia after intrathoracic operations. This is due to acute and severe interference with alveolar ventilation caused by oedema, bronchial irritation and blockage, collapse, and effusions. Such patients are usually obviously cyanosed, and oxygen therapy is given until cyanosis is relieved. However, precise measurement of the arterial blood saturation in these patients can be of great help in the conduct of such cases. More studies of post-operative arterial oxygenation are needed to increase the knowledge of the hazards of various surgical procedures.

Again, arterial blood studies are most useful in the treatment of patients with chronic respiratory diseases who are suffering from acute pneumonic infections. The carbon dioxide content or tensions are particularly valuable in helping to assess the risk of carbon dioxide retention when oxygen therapy is given (Donald, 1949).

Finally, the only method of demonstrating deficient blood oxygenation at rest in early and moderate emphysema is that of measuring the alveolar-arterial oxygen tension gradient. This is greatly increased even in patients with what seems to be relatively normal arterial blood saturation (90–94%).

Exercise Studies

The fact that considerable alveolar underventilation or limitation of the oxygen diffusing capacity causes only very moderate depression of the arterial blood saturation at rest would appear to make this approach unfruitful if blood-tension studies are not available. However, it is fortunate that limited diffusing capacity can be demonstrated by increasing the oxygen demands of the body by brisk exercise. Any inability to increase oxygen transfer in the face of increased oxygen demands will cause dramatic arterial-blood desaturation. This inability to transfer increased quantities of oxygen to the blood is due to a decreased effective blood–gas interface or, more rarely, interference with oxygen diffusion into the alveolar capillary. Thus marked arterial desaturation on exercise may be due to faulty gas or blood distribution, rendering large amounts of lung relatively functionless (emphysema, bronchial obstruction), by disease destroying large amounts of lung tissue (extensive tuberculosis, cystic disease, etc.), or by pathological infiltration of the alveolar wall. The ability to maintain normal arterial oxygenation in the face of increased oxygen demands is therefore a remarkable test of overall respiratory efficiency and actual amount of functioning lung. Arterial blood studies are carried out during various standard exercises (walking, step-test, treadmill), but this relatively simple method of assessing overall lung function is still in its infancy. As in this method study is made of the change or otherwise of arterial saturation, it is likely that oximetry may be of great help and render the test even more accessible to the practising physician.

Finally these various functions of the lungs can now be studied and to some extent assessed quantitatively. Nevertheless, although great progress has been made, mainly by academicians, the true value of these various concepts and methods of assessment of respiratory function will not be known until they are understood and used by practising chest surgeons and physicians, who can then reject, endorse, and advance in the light of real practical experience.

General Summary

The function of the lungs is defined. The importance of lung ventilation and circulation bringing blood and gas in close contact in all alveoli so that efficient gas exchange occurs is emphasized.

The various methods of assessing ventilatory function are discussed. The determination of the lung volumes and ventilatory capacity is described and the greater value of the more dynamic measurements emphasized. The relationship of the volumes ventilated to the ventilatory capacity present in the causation of ventilatory discomfort or dyspnoea is discussed.

The important features of the pulmonary circulation are detailed and the disturbances of this circulation in lung disease, and their effect upon the right ventricle, are described.

Finally, the problem of oxygen transfer and blood oxygenation is considered. It is emphasized that this depends upon the efficient distribution of gas and blood and the proper correlation of alveolar ventilation and circulation throughout the lungs. The diffusion of oxygen across the pulmonary membrane is considered. The theoretical concept of ideal distribution of blood and gas is elaborated and the application of this concept to the measuring of the efficiency of the lungs in this respect, both in health and in disease, is described. The diffusion gradients in the alveoli and the diffusing capacity of the lungs are also considered in both normal and abnormal subjects. The value and future of arterial blood studies in pulmonary disease is discussed.

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THROMBO-ANGIITIS OBLITERANS

CLINICAL DIAGNOSIS AND CLASSIFICATION OF CASES

BY

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"Thrombo-angiitis obliterans is a segmental, inflammatory obliterative disease of the arteries and veins which occurs almost exclusively in young men, involves the extremities, and rarely the viscera also, and produces ischaemia of tissues and frequently gangrene."—Allen, Barker, and Hines (1946).

In 1908 Buerger suggested the name thrombo-angiitis obliterans for a disease of the peripheral arteries which he had studied in eleven lower limbs amputated for "presenile spontaneous gangrene." He did not claim that he had described a new disease, but gave due credit to earlier writers, notably von Winiwarter (1879), who had described the condition under other names. Nevertheless it was largely due to Buerger's (1908, 1924) publications that the disease became a recognized clinical entity, and the name which he suggested, or its eponymous alternative "Buerger's disease," came to be generally used. Since 1908 the literature on thrombo-angiitis obliterans has become extensive; among the more important contributions are the American monograph by Brown and Allen (1928) and, in this country, the papers by Parkes Weber (1916), Telford and Stopford (1924, 1935), and Telford (1937).

As a result of the attention thus focused on the disease it has become customary to classify patients with symptoms of occlusive disease of the arteries of the limbs into two groups: (1) a group of young patients in whom the diagnosis is thrombo-angiitis obliterans, and (2) an older group in whom the arterial occlusion is thought to be secondary to atheroma (arteriosclerosis obliterans). Although the patient's age is regarded as an important factor in deciding his grouping, it is recognized that there are other fundamental differences between the two conditions (Table I). There is, however, no unanimity

TABLE I.—*Differential Diagnosis of Thrombo-angiitis Obliterans and Arteriosclerosis Obliterans*

Feature	Thrombo-angiitis Obliterans	Arteriosclerosis Obliterans
Age at onset of symptoms	Usually under 35 years; rare over 40 years	Usually over 50 years
Sex	Almost exclusively males	Preponderantly males, but not rare in females
Distribution	Upper limbs often involved	Upper limbs seldom involved
Venous involvement ..	Superficial phlebitis in about 40% of cases	Rare
Blood pressure	Normal	Frequently elevated
Association with diabetes	Rare	Frequent
Radiography	Vessels seldom calcified	Vessels often calcified
Biochemistry	No constant abnormality	Blood cholesterol and total fats often high
Pathology	Acute or subacute "inflammatory" lesions	Degenerative lesions with benign thrombosis

regarding the age which separates the two groups. Buerger (1924) described thrombo-angiitis obliterans as a disease which begins in the twenties or early thirties, and the average age at the onset of the disease in his cases was 32 years and 5 months. Brown and Allen (1928) stated that 90% of cases of thrombo-angiitis obliterans occurred between the ages of 20 and 50 years. The average age in Telford and Stopford's (1935) series of 48 cases was 45 years, and Telford (1937) said, "A diagnosis of thrombo-angiitis obliterans may be made with some confidence in patients up to 45 years or even 50." Lewis (1936) thought that the onset of thrombo-angiitis usually occurred in the thirties, Homans (1939) stated that the disease occurred in young men between the ages of 20 and 40 years, and Wright (1948) said that all patients have symptoms before 55 and most before 45. The opinion of Allen *et al.* (1946) was that "it is fairly safe to consider that if the symptoms of chronic occlusive arterial disease begin after the patient is 50 years of age the lesion is arteriosclerosis, and if they begin before the age of 40 years the lesion is thrombo-angiitis obliterans."

Current views regarding the differential diagnosis between the two groups may be summarized as follows: a diagnosis of thrombo-angiitis obliterans may be made with some certainty in the case of a male patient suffering from occlusive arterial disease who was under the age of 35 years at the time of his initial symptoms, gives a history of superficial phlebitis, and has involvement of the arteries of the upper limbs; if the patient is over 50 years, if the disease is confined to the lower limbs, if there is some degree of hypertension, and if radiographs of the affected limbs reveal calcification in the walls of the arteries, then arteriosclerosis may be diagnosed confidently. There are many patients with occlusive arterial disease in whom the clinical picture is not sufficiently clear-cut to permit of these definite diagnoses. These patients are in the age group between 35 and 45 years; although their blood pressure is normal and they do not have calcified vessels, they do not give a history of

phlebitis and the disease is apparently confined to one or both lower limbs. Hitherto the tendency has been to regard these patients as suffering from thrombo-angiitis obliterans rather than arteriosclerosis obliterans, although the natural history of their disease is often different from that observed in younger patients who show all the classical features of thrombo-angiitis obliterans.

An attempt to clarify this situation has recently been made by Boyd and his colleagues (Boyd *et al.*, 1949; Boyd, 1950), who have proposed a new classification of obliterative arterial disease of the lower limbs:

1. *Traumatic Arterial Thrombosis.*

2. *Juvenile Obliterative Arteritis.*—"This comprises a group of cases corresponding to those described by Buerger, and the condition may be a pathological entity."

3. *Primary Popliteal Thrombosis.*—A benign condition in which a local thrombosis develops in the popliteal artery as a result of trauma to the vessel where it runs behind the knee-joint.

4. *Senile Obliterative Arteritis.*—An inclusive term which covers all forms of arterial disease generally referred to as arteriosclerosis; it accounts for 95% of all cases of occlusive arterial disease, and the cases may be subdivided into the following groups: (*a*) diffuse obliterative arteritis; (*b*) secondary popliteal thrombosis; (*c*) secondary femoral thrombosis; and (*d*) distal type.

It is apparent that many cases which would be regarded by most authorities on peripheral vascular disease as instances of thrombo-angiitis obliterans are classified by Boyd under the headings of primary popliteal thrombosis and senile obliterative arteritis.

Clinical Material

Consideration of these facts has led me to review the case histories of 85 patients who were first seen between 1941 and 1947, and in whom a diagnosis of thrombo-angiitis obliterans was made. There were 84 males and one female in the series and their ages ranged from 21 to 56 years. All were smokers, but few could be regarded as heavy smokers. The majority of the patients were Scots, but the series included a Belgian, a Dutchman, and an Italian; only one patient was of the Jewish race. Many of the cases have been included in the recent clinical review published by Lynn and Burt (1949); most of these have been followed for several years, and the natural history of their disease is therefore known. Lynn and Burt dealt with the clinical features, the treatment, and the results of treatment, and these aspects will not be reconsidered.

Because of the importance which has been attached to the patients' age in regard to the diagnosis of thrombo-angiitis obliterans the cases have been divided into three groups according to their age at the onset of the disease (Table II). Superficial thrombophlebitis occurred in 27

TABLE II.—*Clinical Material*

	Age Group			Totals
	Under 35	35–45	Over 45	
No. of cases	39	37	9	85
No. with superficial phlebitis	12	13	2	27
No. with involvement of upper limbs	15	8	2	25
No. with hypertension (B.P. 150/90)	4	8	3	15
No. with pathological confirmation of diagnosis	12	8	2	22

cases, an incidence of 32%, which is similar to that usually quoted (Buerger, 1924; Allen *et al.*, 1946; Edwards, 1949). In 25 cases (29%) there was clinical evidence of involvement of the arteries of the upper limbs, a lower incidence than that given by Allen *et al.* (1946) and Farber and McLain (1951).

Fifteen patients had a blood pressure higher than 150/90 mm. Hg; the highest pressure was 190/100 in a patient in whom the diagnosis of thrombo-angiitis obliterans was confirmed. In most of the cases, and in all patients over the age of 40, radiographs of the affected limbs were taken; these did not reveal calcification in the walls of the arteries. Pathological confirmation of the diagnosis was obtained in 22 cases—by examination of material obtained by amputation (18 cases), at necropsy (3 cases), and by biopsy of a thrombosed vein (1 case). In two other cases necropsies performed since 1947 have shown that the arterial lesions were due to atheroma and not to thrombo-angiitis obliterans.

Clinical Classification

Several clinical classifications of cases of thrombo-angiitis obliterans have been suggested. Brown and Allen (1928) described 12 clinical types, Learmonth (1937) stated that cases could be divided into four groups, and Allen *et al.* (1946) mentioned nine clinical types and four groups according to the course of the disease. None of these classifications was entirely satisfactory for the present series, which has been subdivided into five groups (Table III).

TABLE III.—*Clinical Classification*

Clinical Type	Age Group			Totals
	Under 35	35–45	Over 45	
Acute	8	4	1	13
Episodic	16	11	1	28
Slowly progressive	7	11	7	25
Acute arterial occlusion	5	10	0	15
Upper limbs	3	1	0	4

1. *An "Acute" Group* (13 cases).—In this group the disease began either suddenly or insidiously and progressed rapidly; within a year of onset gangrene was extensive enough to necessitate either a major amputation or the loss of more than digits.

2. *An "Episodic" Group* (28 cases).—The history of the disease was punctuated by a series of episodes separated by months or years, each episode corresponding to a wave of thrombosis, either venous or arterial. Between the episodes the disease was quiescent and the patients were apparently well except for such residual disabilities as were left by the previous wave of thrombosis.

3. *A "Slowly Progressive" Group* (25 cases).—Intermittent claudication affecting the muscles of the leg was the first symptom of the patients in this group. The condition progressed slowly with gradual shortening of the "claudication distance"; nutritional changes and gangrene were late manifestations.

4. *An "Acute Arterial Occlusion" Group* (15 cases).—The onset was sudden and indicated that the patient had suffered an acute occlusion of either the femoral or the popliteal artery. This did not result in gangrene, but thereafter the patient had intermittent claudication in the affected limbs and the foot blanched unduly on elevation.

5. *An "Upper Limbs" Group* (4 cases).—In this group the disease was either confined to the upper limbs or the symptoms in the hands were of major importance and only minimal signs of disease were found in the lower limbs.

The first three groups represent well-recognized types of thrombo-angiitis obliterans. It will be noted that the incidence of the acute and episodic cases was greatest in patients under 35 years of age, and that in only one patient in each group did the disease begin after the age of 45. The age distribution of the slowly progressive type of case was different: the cases were more evenly distributed throughout the three age groups, and the greatest incidence was in the 35–45 period. The incidence of superficial phlebitis in these cases was low (only 3 cases out of 25), and none of the patients had involvement of the upper limbs. There is therefore some reason for questioning the diagnosis of thrombo-angiitis obliterans in these cases.

The fourth clinical group is of particular interest. Ten of the 15 cases in this group were in patients whose ages were between 35 and 45 years, and it is in patients of that age that the problem of diagnosis is most difficult. Opinions differ on whether acute occlusion of a major artery occurs

in thrombo-angiitis obliterans. Telford (1937) gave an excellent description of this type of case, and expressed the opinion that the occlusion was due to an embolus—"the embolus having been derived from some patch of atheroma or calcification in a vessel proximal to the popliteal. That they are not true thrombo-angiitis obliterans is evident from the fact of the sudden very painful onset and from the observation that the other leg is apparently normal." Klostermeyer (1941), on the other hand, suggested that many cases of thrombo-angiitis obliterans begin with occlusion of a major artery. Allen *et al.* (1946) recognized a type of thrombo-angiitis obliterans with sudden arterial occlusion, but they also stated that "cases in which acute and extensive arterial occlusion occur are uncommon." According to Boyd's classification, cases of this type would be examples of primary popliteal thrombosis or of senile obliterative arteritis with secondary thrombosis of the femoral or popliteal arteries.

At least some of the patients over the age of 35 who presented with signs of an acute arterial occlusion probably do belong to the latter category. The five patients under the age of 35 are more difficult to classify. Three of these cases were reported by Learmonth *et al.* (1944) as instances of "localized arterial thrombosis of undetermined origin." The fourth case, which we reported at that time, is now included in the upper-limb group because the brachial artery was affected. The subsequent histories of these four patients are illuminating: two (Cases 1 and 4) have had further episodes of thrombosis, both venous and arterial, and therefore would now qualify for inclusion as cases of thrombo-angiitis obliterans with an episodic course; of the other two, one (Case 2*) has had no further trouble, and the fourth (Case 3) is untraced. The natural history of these cases is therefore different from Boyd's conception of primary popliteal thrombosis; he regards the latter as a benign condition, and states that he has followed patients for ten years and found no further evidence of arterial disease (Boyd, 1950).

Most writers agree that involvement of the upper limbs occurs more often in thrombo-angiitis obliterans than in arteriosclerosis obliterans. Boyd *et al.* (1949), however, state that juvenile obliterative arteritis (which they regard as corresponding to Buerger's original description of thrombo-angiitis obliterans) is confined to the lower limbs, and that involvement of the upper limbs is more characteristic of senile obliterative arteritis. In the present series 25 patients had symptoms or signs of arterial disease in the upper limbs (see Table II). In four patients the symptoms and signs in the hands were of major importance, and evidence of the disease in the lower limbs had to be sought; three of these patients were under 35 years of age and one was in the 35–45 age group. All were found to have occlusive arterial disease in the lower limbs, but only one gave a history of an attack of superficial phlebitis.

Classification According to the Site of the Arterial Lesion

An alternative method of classifying cases of occlusive arterial disease is according to the site of the arterial lesion. Clinically it is possible to recognize two distinct types (Boyd, 1938). (1) A proximal type: in this group the occlusion is in the main artery of the limbs, claudication in the calf muscles is the main symptom, and postural colour changes in the foot are pronounced. (2) A distal type: the disease appears to begin in the arteries of the foot, pain in the foot either on exertion or at rest is the presenting symptom, the progress of the disease is more rapid than in the preceding group, and ulceration and gangrene are common.

When an attempt was made to divide the cases in the present series into these two types it was found that, although some cases could be allocated to one or other of the groups with certainty, there were a larger number in which the clinical findings and special investigations indicated that both proximal and distal vessels were occluded. These cases therefore constitute a third group, which may be called the "mixed type" (Table IV).

TABLE IV.—*Classification According to Site of Lesion*

Site of Lesion	Age Group			Totals
	Under 35	35–45	Over 45	
Proximal type	7	9	3	19
Distal ,, ...	18	11	1	30
Mixed ,, ...	14	17	5	36

1. *The Proximal Type* (19 cases).—The outstanding feature of the cases in this group was that at the initial examination the disease appeared to be confined to one lower limb. Fourteen of the patients presented clinically as instances of acute arterial occlusion (see Table III); the remainder gave a history which suggested that the disease was slowly progressive, but examination indicated that they had a localized block in a main artery.

2. *The Distal Type* (30 cases).—In 22 cases both lower limbs were affected when the patient was first seen; in eight cases the disease was unilateral. The cases were evenly distributed through the acute, episodic, and slowly progressive clinical groups.

3. *The Mixed Type* (36 cases).—In all the cases in this group the disease was bilateral; in some, distal vessels only were occluded in one leg and both distal and proximal vessels in the other lower limb. As in the second group, the cases were distributed throughout the acute, episodic, and slowly progressive clinical groups, but the greatest number (15) were in the episodic group.

Buerger's (1908, 1924) descriptions of thrombo-angiitis obliterans clearly indicate that he regarded the disease as one which affected principally the arteries of the foot and leg, and which tended to spread proximally, often with a patchy distribution to involve the popliteal and, occasionally, the femoral vessels. Certainly the majority of cases of thrombo-angiitis obliterans begin as a distal arteritis, although often in the early stages the correct diagnosis is not made, and by the time the true condition is recognized the disease has spread to the proximal vessels. It is unusual for the initial symptoms to be those of acute occlusion of a main vessel, and when this occurs the diagnosis is more likely to be arteriosclerosis obliterans. Nevertheless, experience with some of the cases in the proximal group has shown convincingly that thrombo-angiitis obliterans does occasionally present in this manner: if the patient with an acute arterial occlusion is under 35 years of age the possibility that the cause is thrombo-angiitis obliterans should not be too readily dismissed. If, when the patient is first seen, both distal and proximal vessels are occluded it is often impossible to determine the level at which the obliterative process began, and clinical diagnosis is more difficult.

Conclusion

It is apparent from this study that the clinical diagnosis of thrombo-angiitis obliterans is not a simple problem. Much of the present confusion is due to the fact that Buerger used the term "thrombo-angiitis obliterans" in the first instance to describe the pathological lesion which he found in the arteries of the original eleven amputated limbs; only later did he apply the name to a group of clinical cases. It was assumed by Buerger (1924) and others that all patients presenting features similar to those of his original cases were suffering from the same disease. The symptoms and signs of obliterative arterial disease, however, depend not so much upon the pathological nature of the occlusive process as upon the distribution and extent of the lesions in the arterial tree. With the possible exception of superficial phlebitis none of the clinical features of thrombo-angiitis obliterans is pathognomonic. The diagnosis therefore must often depend upon the natural history of the patient's illness. In the past too much emphasis has been placed upon such criteria as race, age, and involvement of the upper limbs.

*Case numbers refer to those used by Learmonth *et al.* (1944).

Buerger's original contention that the disease occurred most frequently in the Jewish race has long been disproved. Pathologists have often commented upon the fact that atheromatous changes are sometimes found in the arteries of young adults who come to necropsy as a result of fatal accidents and other conditions which do not primarily affect the cardiovascular system. If proof were required that such changes can be the basis of obliterative arterial disease it is amply provided by the studies of Newman (1946, 1951) and Poe (1947) on cases of coronary artery occlusion in young adults. Newman reviewed 100 cases of coronary occlusion which occurred in patients under 35 years of age, and found that in all of them the pathological changes in the coronary arteries were similar to those found in older patients—namely, atheroma. What happens in the coronary arteries may also occur in the arteries of the limbs, and therefore the possibility of arteriosclerosis obliterans, the pathological basis of which is atheroma, cannot be dismissed merely on account of the patient's youth. Involvement of the arteries of the upper limbs is not uncommon in cases of arteriosclerosis obliterans. The two criteria which remain as reliable indications for a diagnosis of thrombo-angiitis obliterans are its constant association with tobacco-smoking and its predilection for the male sex. The value of these criteria is lessened by the fact that smoking is an almost universal habit, and that, except in diabetics, all forms of obliterative arterial disease are commoner in men.

In its classical form thrombo-angiitis obliterans presents as an acute or episodic type of obliterative arterial disease occurring in a young adult male who smokes; it begins in the arteries of the lower leg or foot, may be preceded or accompanied by superficial migratory phlebitis, and is often associated with fungus infection of the feet. In cases of this type pathological examination of the affected arteries or veins almost invariably reveals lesions similar to those found by Buerger in his original cases. Many cases do not conform to this classical picture, and the clinical diagnosis can then be only a tentative one. Nevertheless, as Buerger (1924) states, "a careful clinical study of thrombo-angiitis obliterans will dissipate all doubt as to the possibility of separating this disease, as a clinical entity, from the other types of organic vascular disease as well as from all those neurogenic varieties of vasomotor and trophic disorders that may be clinically confounded with it."

Summary

The criteria necessary for a clinical diagnosis of thrombo-angiitis obliterans are reviewed with particular reference to a personal series of 85 cases. The view is put forward that the diagnosis should be based principally upon knowledge of the natural history of the disease and that such factors as race, age, and involvement of the arteries of the upper limbs are of secondary importance.

The majority of the patients were under the care of Sir James Learmonth, to whom I am indebted for the opportunity to study them. I wish to thank Dr. C. C. Burt for help in case-taking and for providing me with follow-up data on many of the cases.

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SIMPLIFIED METHOD OF DRUG TREATMENT FOR THYROTOXICOSIS

USING A UNIFORM DOSAGE OF METHYL-THIOURACIL AND ADDED THYROXINE

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The thiouracil drugs are now used widely both for the pre-operative management and for the prolonged medical control of thyrotoxicosis. The use of these drugs over long periods carries two potential disadvantages; first, the possibility of overdosage, which will cause further goitre enlargement and worsening of the eye signs along with subclinical or obvious myxoedema; and, secondly, the remoter risk of agranulocytosis or other lesser toxic effects. It is known from animal experiments that goitrogenesis during antithyroid drug administration depends on the increased output of pituitary thyrotrophin which is induced when the level of thyroid secretion is lowered, for it can be avoided by giving enough exogenous thyroxine (Purves, 1943; Astwood *et al.*, 1943) or by hypophysectomy (Griesbach *et al.*, 1941). The worsening of the eye signs of Graves's disease, which may also be seen as a manifestation of overdosage during thiouracil treatment, probably depends on the same mechanism. Thus the risks of thiouracil overdosage are those of its over-suppression of thyroid function.

Clearly these risks of overdosage should be avoidable either by adjusting the thiouracil dosage to levels just short of those which over-suppress thyroid function or merely by daily supplemental administration of thyroxine or thyroid. The former is the basis of the usual clinical practice of adjusting the thiouracil dosage to the patient's individual requirements; but this requires frequent and careful supervision, which can readily worsen the nervous state of such patients. We have therefore attempted to evolve a simpler procedure by giving thyroxine with the methylthiouracil and so adopting the latter method of avoiding the risks which may follow undue suppression of thyroid function. A uniform basic dosage scheme giving both drugs should suffice, unmodified, for most cases if it provided enough methylthiouracil to block thyroid hormone production

adequately in all cases and also supplied enough thyroxine for the normal daily needs of thyroxine. If the basic or standard dosages were correctly chosen the drug control should consist simply in watching the goitre size and adding thyroxine if goitre enlargement appears; while, to the occasional cases in which thyrotoxicosis does not seem controlled by this basic dosage, extra methylthiouracil could be given without any added risk of goitrogenesis. We have combined the basic dosage scheme into a single pill, so that one methylthiouracil co. pill is given thrice daily during the maintenance phase; and extra thyroxine is prescribed if goitre enlargement appears.

Present Investigation

A trial of this procedure seemed necessary to ascertain not only the optimal dosage schedule and whether it avoided the risks of thiouracil overdosage, but also whether its avoidance of over-suppression of thyroid function altered the frequency of permanent remissions after termination of the treatment. We have analysed the preliminary results of this treatment in our first 51 patients, particularly as regards the avoidance of goitrogenesis and of worsening of the eye signs during treatment, and the remission rate obtained after completion of treatment, comparing these with the published results of other methods of prolonged thiouracil treatment.

Selection of Cases.—This analysis concerns all our 51 patients (10 male, 41 female) who started this prolonged thiouracil treatment before August, 1951, and completed it before February, 1952; in all patients the diagnosis of thyrotoxicosis had first been confirmed by radio-iodine excretion test (Fraser *et al.*, 1952). All cases have been followed for one year or more after treatment ceased. The ages of these patients ranged from 11 to 68 years, with an average of 37.7 years. At first all cases of thyrotoxicosis were treated with methylthiouracil co. unless the patient expressed a preference for surgery. Later, radio-iodine treatment was used for all patients over 45 years of age and for a few younger subjects judged to have a life expectation of less than 20 years. Also, with increasing experience, surgical treatment was preferred for young patients with an initially large or nodular goitre or with evidence of a marked allergic diathesis, and for those patients considered insufficiently reliable for a prolonged drug treatment which needs precise regularity.

Methods

For the treatment two strengths of methylthiouracil co. pills were used—100 and 50 mg. During the evolution of this procedure there has been a change in the amount of thyroxine added to these pills, and so in the need for added thyroxine. We now believe that the new methylthiouracil co. pills, containing 0.1 mg. of L-thyroxine against the 0.075 and 0.05 mg. of the "old" methylthiouracil co. pills, provide the optimal added thyroxine (0.1 mg. t.d.s.) for the basic maintenance dosage schedule; clearly, giving the same dosage of these two drugs separately should provide equivalent control.

During the induction phase the patients received two 100-mg. methylthiouracil co. pills thrice daily until they were considered to be restored to a euthyroid state; this phase usually lasted six to eight weeks. They were then put on a maintenance dosage of either 50 mg. or 100 mg. (usually the former) of methylthiouracil co., taken in each case three times daily. Additional thyroxine was given at the first sign of enlargement of the thyroid gland and sometimes if the eye signs were initially severe.

Most cases were treated as out-patients, but in a few instances treatment was begun in hospital. Patients were seen at intervals of one to three months, when progress was assessed mainly from the body weight, the state of the circulation, the eyes, and the size of the thyroid gland. All patients were warned to report to hospital if a sore throat or other illness supervened. A white-cell count was done at the start of treatment but was not repeated unless any such symptoms developed.

The course of treatment was for a minimum of nine months, but was prolonged if the patient's physical state was unsatisfactory or if worries or stress were known to exist. Patients completing the course were treated for one month with thyroxine, 0.1 mg., and potassium iodide, 1/6 gr. (11 mg.) daily, the former to depress thyrotrophic hormone production during the restoration by the latter of the thyroid's depleted iodine store. All patients were reassessed clinically at three and twelve months after treatment, on one or both of which occasions a radio-iodine test was performed.

Results

The subsequent analysis concerns the 32 patients who completed a full course of nine months' treatment; 19 failed to complete a full course for the following reasons:

Agranulocytosis (later recovered)		3
Patient ceased attending		9
Other treatment preferred		7
Chosen for I^{131} therapy	3	
Surgery for large goitre	3	
Surgery because of cardiac state	1	

Status After Ceasing Treatment (Remission Rate).—The results are shown in Table I; all of the 18 remitted cases have been observed for 12 or more months. They appear to be quite well and free from clinical signs of thyrotoxicosis, though the radio-iodine test suggested that three had hyperactive thyroids. One of these patients also had nervous symptoms, associated with an unhappy domestic situation. In six patients there were residual eye signs—two had minor ocular paresis and four had only slight degrees of exophthalmos or lid retraction. Of the 14 (44%) patients who relapsed, six did so in the first six months, six between 6 and 12 months, and two later. It seemed that the relapsed cases had had a longer illness before treatment, that they included more patients with

TABLE I.—*Clinical Status Six Months or More after Finishing Prolonged Treatment with Methylthiouracil Co.*

Well, and normal I^{131} test	9 (28%)
,, ,, I^{131} test, but residual eye signs	6 (19%)
,, but abnormal I^{131} test	3 (9%)
Thyrotoxicosis relapsed	14 (44%)
Total	32

TABLE II.—*Goitre Size and Eye Signs During and After Prolonged Treatment with Methylthiouracil Co.*

	Goitre Size			Eye Signs of Graves's Disease			
Grading Before Treatment:		Less Than 2½ Times Normal (21)	More than 2½ Times Normal (11)		Severe (6)	Mild (17)	Nil (9)
Temporary change during treatment	Enlargement controlled by extra thyroxine	(7)	(7)	Possible worsening	(2)	(1)	—
Status on finishing treatment	Smaller than initially, and:			Nil	—	13	9
	Less than 2½ times normal	20	5	Mild (lid retraction or mild exophthalmos)	3	3	—
	More than 2½ times normal	—	6	Severe:			
	Larger than initially	1	—	Ptosis only	—	1	—
				Muscular paresis	3	—	—
				Significant worsening	—	—	—

nervous or unstable personalities, and that they had more often (in 9 out of 14) had some persisting cause for anxiety during the period after ceasing treatment.

Control of Goitre Size.—As is shown in Table II, the size of the goitre increased temporarily during treatment in almost half the cases (14 out of 32), but when extra thyroxine was given the added enlargement almost always subsided. In only one case did the goitre size at the end of treatment exceed that noted at the start of treatment, and in 25 out of the 32 cases the goitre was then judged to be less than two and a half times normal size. Among the 19 patients not completing a full course of treatment there were three who had surgical treatment for a large goitre. All of these patients had initially large goitres which had at first further enlarged during thiouracil treatment; one case is of particular interest in that the goitre continued to enlarge despite the administration of L-thyroxine totalling 0.6 mg. daily. After surgical removal the thyroid in this case was found to weigh 300 g. This was the only case in the whole series in which thyroxine up to this dosage failed to prevent further goitre enlargement.

The Eyes During Treatment.—Eye signs were initially present in 23 patients: in 17 they were mild and in six severe (that is, including ocular palsy and/or obvious conjunctival congestion). As shown in Table II, in no case did eye signs develop or worsen significantly during treatment. The possible worsening noted at some stage in three patients was only temporary and slight. At the end of treatment relatively minor eye signs persisted in all six of those patients who had originally had severe eye signs and in four other patients. In six of these ten cases this was either mild exophthalmos or lid retraction, though two still had some diplopia and one had slight ptosis. Extra thyroxine was given to three of the patients with initially severe eye signs, so that their total daily thyroxine ranged from 0.3 to 0.6 mg.

Adequacy of Basic Dosage Schedule.—Suppression of Thyrotoxic Features:—During treatment these features were controlled in all patients, though in a few the usual maintenance dose of 50 mg. of methylthiouracil co. three times a day had to be increased to 100 mg. to achieve this. In one patient there was at first some doubt whether control was satisfactory; but as the symptoms persisted despite 7.2 g. of methylthiouracil daily it was concluded that these symptoms were of nervous and not thyrotoxic origin. *Use of Extra Thyroxine:*—At some stage 18 patients were given 0.1 to 0.3 mg. of additional thyroxine daily, apart from that included in the old compound tablets. This was prescribed in 15 instances because of goitre enlargement and in three because of severe eye features. In three patients this additional thyroxine was continued because pregnancy supervened. Extra thyroxine was given for less than three months in five cases and for longer periods in the remainder. Only five patients had received an average daily total of more than 0.3 mg. of L-thyroxine, which is the amount they would have received using only the new compound tablets now in use.

Control During Pregnancy.—Pregnancy occurred successfully in three patients. One patient, however, gave birth to a child with a large goitre, but this subsided rapidly with small doses of thyroxine for three months, and the child has since developed normally. The mother in this case had been maintained throughout most of her pregnancy on methylthiouracil co., 100 mg. t.d.s. (which included 0.225 mg. L-thyroxine daily) with 0.1 mg. t.d.s. of extra thyroxine until the last four weeks before delivery, when by accident the extra thyroxine was omitted. After this experience we have been careful to maintain pregnant patients on small doses of methylthiouracil co. (usually 50 mg. t.d.s.) with relatively large doses of added thyroxine (usually 0.3 mg. daily), and the results have been satisfactory. Only one child was breast-fed, and during the period of lactation the mother was maintained on methylthiouracil co., 50 mg. t.d.s., with 0.3 mg. of extra thyroxine daily.

Discussion

This preliminary report has been made on a small series because it suggests that control of thyrotoxicosis is possible by this fairly standardized and simple procedure, using methylthiouracil combined with thyroxine.

With one exception, which required surgical treatment, goitrogenesis has been adequately averted—provided extra thyroxine was prescribed if indicated. In no cases have the eye signs significantly worsened during or after therapy. Very few other reports give more than brief mention of the effects of prolonged antithyroid drug treatment on the goitre size and eye signs. Williams (1946), however, found that thyroxine was necessary because of goitrogenesis or worsening of the eye signs in 31 out of 247 cases treated with thiouracil; and among those patients receiving prolonged treatment the goitre enlarged in 7%. Dunlop and Rolland (1950) found that slight goitre enlargement "was not uncommon" during methylthiouracil treatment, while Frisk (1948) reported enlargement in 50% of cases. Obviously the frequency of goitre enlargement will depend on the degree of thyroid suppression attained. Astwood (1948) has suggested that it is better to keep the patient at a slightly hypothyroid level; if this is attempted goitrogenesis will probably be a very definite problem.

With this group of cases extra thyroxine was often necessary (in 14 out of 32) to avoid goitrogenesis. Our current practice, however, is to give a larger basic or standard dosage of thyroxine, to provide 0.3 mg. a day. The compound tablets now each contain 0.1 mg. of L-thyroxine with either 100 mg. or 50 mg. of methylthiouracil, so that either strength given thrice daily should provide a maintenance dosage. With this modified or "new" standard dosage extra thyroxine is rarely needed. There should be no hesitation about giving this extra thyroxine (0.1–0.3 mg. a day) in doubtful cases. The thyrotoxic features have usually been controlled with the 50 mg. of methylthiouracil co. thrice daily and always with the 100 mg. strength thrice daily. Thus the compound thiouracil tablets have provided satisfactory control in every case, and the use of these tablets does simplify the treatment. Ordinarily the patients follow a routine schedule and are maintained on 50 mg. of methylthiouracil co. three times a day. If the control of thyrotoxicosis then seems defective this is changed to the stronger compound tablets, 100 mg. three times a day, the only other dosage control required being to give extra thyroxine if goitre enlargement is noted. In a straightforward case there is no necessity for the patient to be seen more often than at three-monthly intervals during maintenance treatment.

When one considers the relapse rate there is less cause for satisfaction, though our results are probably similar to those achieved with the usual prolonged thiouracil treatment. Admittedly the results reported in the literature vary widely, and it is difficult to know which figures to choose for comparison. Starr *et al.* (1949), using propylthiouracil, failed to achieve a single lasting remission, whereas Frisk (1948), using methylthiouracil, claims a remission rate of 90%, though some of his patients had been followed for only six months after treatment, and several patients had required two courses of treatment. Williams *et al.* (1947) and Dunlop and Rolland (1950) followed patients for a year or more after prolonged thiouracil treatment, and reported remission rates of 46% and 47% respectively, which compares with our remission rate of 56%. Other recent reports claim remissions in 41% (Stirrett *et al.*, 1952), 70% (Murray, 1950), 85% (Astwood, 1948), and 88% (Iversen, 1951, but here relapses within six months of stopping treatment were excluded).

Final evaluation of these drugs must await further experience; possibly both case selection and variations in the technique of using thiouracil may have contributed to the varying results. A drug treatment is needed for those

patients who do not desire surgery and cannot have radio-iodine, and is used with many other patients for varying reasons.

We would suggest that the procedure outlined above, while simplifying the management of such cases, diminishes the risk of goitrogenesis and of worsening of the eye signs without impairing the therapeutic effects.

We should expect the procedure to be similarly suitable for preparing the thyrotoxic patient for operation, provided iodide is given in addition over the last two weeks. We are at present investigating the latter method.

Summary

A preliminary report is made of the practicability of treating thyrotoxicosis with both methylthiouracil and thyroxine to simplify the control of dosage. The results were apparently as satisfactory as the published results obtained with antithyroid drugs alone.

A basic standard dosage was used (enough methylthiouracil to control all but exceptional thyrotoxicosis and the minimal normal thyroxine requirements—that is, methylthiouracil, 50 mg., and L-thyroxine, 1 mg., thrice daily); this standard dosage, unaltered, suffices for the maintenance treatment of most patients, provided signs of goitre enlargement are sought and when seen are countered by giving additional thyroxine. If the adequacy of the control of thyrotoxicosis is doubted the methylthiouracil dose can be increased.

Among the first 32 cases completing a course of nine or more months of such treatment, in 18 (56%) the thyrotoxicosis was still fully remitted one year later, in no case had the eye signs significantly worsened, and in all except one the goitre size had decreased.

We are indebted to Glaxo Laboratories Ltd., who supplied the pills for this trial.

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Aided by a grant from the National Institute of Mental Health of the United States Public Health Service, the Yale Centre of Alcohol Studies recently surveyed current American work on alcoholism. Their findings, originally printed in the *Quarterly Journal of Studies on Alcohol* (1952, **13**, 421–511), have now been published as a separate booklet entitled "Alcoholism, 1941–1951: A Survey of Activities in Research, Education, and Therapy." Although the main emphasis is naturally on American studies in this field, much of the material included in the book is of general application and likely to interest workers elsewhere. The book is comprised of six sections each written by members of the staff of the Yale Centre, and with an introduction by the Director of the Centre. The sections are entitled: Sources of Scientific Information; the Status of Physiological Knowledge; Social Science Research; the Treatment of Alcohol Addiction; Programmes on Alcoholism in the United States, 1952; and Activities of State Departments of Education concerning Instruction about Alcohol. Copies of the book may be obtained from: *Quarterly Journal of Studies on Alcohol*, 2162 Yale Station, New Haven, Connecticut, price $1 per copy.

PITYROSPORUM OVALE AND SOME SCALY CONDITIONS OF THE SCALP

BY

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The part played by the organism *Pityrosporum ovale* in the aetiology of a number of conditions of the skin has been much debated. By some it is held to be the prime and only cause of dandruff of the scalp and "seborrhoeic" eczema of the body; by others it is denied that the organism is anything but a harmless saprophyte which thrives under the cultural conditions provided by certain diseases. The problem is not made any easier by the confused and confusing terminology which has been applied to the group of conditions variously labelled as dandruff, pityriasis capitis, seborrhoea, seborrhoeic eczema, pityriasis circinata, the eczemas, etc.; the list could be made very much longer. So far as this paper is concerned, I hope to avoid lengthy discussion of the problems of seborrhoea, male-pattern baldness, and seborrhoeic eczema, and to confine my attention to certain scaly conditions of the scalp. It is not entirely possible to do this, as the three diseases often coexist with the subject under consideration.

Review of the Literature

Sabouraud (1902) held quite firmly that the cause of dandruff, or pityriasis simplex of the scalp, was infection with *P. ovale*. In addition, when the scalp became infected with an organism variously named the polymorphic coccus of Cedercreutz or the morococcus (Unna), but which seems to be the same organism as the *Staphylococcus epidermis albus* of Welch, the nature of the scaling changes from a dry condition to one which appears to be greasy, and is termed pityriasis steatoides or serosa. To add to the problem the scalp might also be affected with the acne bacillus, held by Sabouraud to be the cause of increased sebaceous secretion on the skin, thus causing an oiliness of the scalp, with an aetiology differing from the supposed greasiness of pityriasis steatoides.

Darier (1920), however, propounding his doctrine of "kerose," was of the opinion that pityriasis capitis is but a manifestation of the underlying state which is characterized by a brownish dirty-yellow complexion, slight thickening and hyperkeratosis of the skin of the centre of the face, scalp, and other areas, and enlargement of the pilosebaceous follicles with hyperkeratosis of their openings. He regarded the kerose as a constitutional condition normal to certain types of person rather than a disease, and that *P. ovale*, the acne bacillus, and the polymorphic coccus grew best on this type of "soil," but were in no way responsible for any disease or for the varying manifestations of kerose.

Sabouraud was not able to culture *P. ovale*, but Macleod and Dowling (1928) cultured an organism which they thought to be *P. ovale*, and which they believed to be the cause of dandruff of the scalp. In addition, by inoculation experiments with their culture on the normal skin they produced lesions which they thought were identical with those of seborrhoeic eczema. However, it was later realized that the organism was not *P. ovale* but *M. pinoyi*, a fact acknowledged by Dowling (1939) himself. Unfortunately the original experiments are still cited in many modern textbooks of diseases of the skin and hair as if they are the proof positive that *P. ovale* is the cause of seborrhoeic eczema and dandruff. Why the later repudiation by Dowling

is not more widely known is difficult to understand, but Savill (1952), a strong supporter of Sabouraud, still writes as if it had never been made.

Templeton (1926) managed to culture the organism and made some scrapings from "normal" scalps and from scalps affected with pityriasis simplex and with oily dandruff. Of the 26 normal scalps it is significant to note that 13 were those of children under 15 years of age. *P. ovale* was present in 69% of these cases which were devoid of dandruff, in 27 out of 28 cases of pityriasis simplex, and in 85% of cases afflicted with oily dandruff. Templeton had some difficulty in deciding where dry dandruff ended and oily dandruff began, and I would agree with his conclusion that the two merge together imperceptibly. It is by no means easy to distinguish the minute details described by Sabouraud, and I suspect that many who describe his classification have difficulty in doing so themselves. Dry dandruff, or pityriasis simplex, is easy to recognize; so also is dry dandruff made greasy by sebaceous secretion. On the other hand, I am by no means convinced of the separate existence of pityriasis steatoides or serosa, which seems to be, as described by Sabouraud, an eczematous condition of the scalp more often to-day called seborrhoeic eczema.

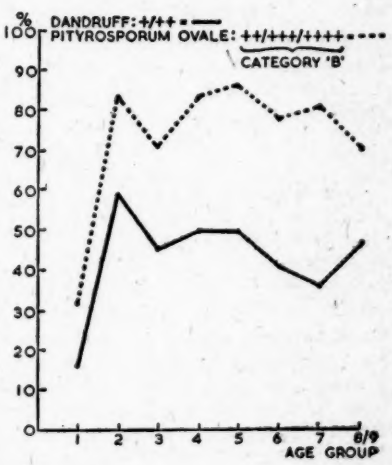
Ota and Huang (1933) cultured *P. ovale*, and, after pointing out that the organism grown by Macleod and Dowling was not the same as their own, they attempted to repeat their experiments. They concluded that *P. ovale* was not the cause of seborrhoeic eczema, as they were unable to obtain more than a transient erythema with their inoculations. Moore and his colleagues (1936) cultured *P. ovale* and believed that they were able to produce lesions of seborrhoeic eczema by percutaneous inoculation, and could recover the organism later from the lesions. Unfortunately it was by no means clear (*a*) why some inoculations "took" and others did not; (*b*) what were their criteria for seborrhoeic eczema; and (*c*) whether the organisms they recovered were the same as those they inoculated or those which were on the skin of the patient before the experiment was started. Kile and Engman (1938) were able to find *P. ovale* in 21 out of 24 cases of seborrhoeic blepharitis, and thought that by inoculation of cultures on to scalps "clinically free from seborrhoeic eczema" they were able to cause scaling, itching, and lesions "like seborrhoeic eczema" after an interval of two weeks, during which the scalp remained unwashed. Unfortunately, again there was a total absence of control experiments, and the results cannot be held to be in any way conclusive.

Bigham (1937) made scrapings and cultures from patients with various scaly dermatoses and scalps, and detected the presence of *P. ovale* and a "yeast-like organism." He was able to find *P. ovale* in 20 control "normal" scalps and in all of seven cases of seborrhoeic eczema. He was also able to recover the organism from the scalps of patients affected with diseases such as psoriasis and pityriasis rosea, so he concluded that the *P. ovale* was not the cause of seborrhoeic eczema. Mackee *et al.* (1938) examined the flora of the scalps of 100 unselected persons and were unable to find any correlation between the incidence of *P. ovale* infection, seborrhoeic eczema, and normal scalps. In further studies Mackee *et al.* (1939) were unable to show any relationship between the type of skin and the presence or absence of various organisms, including *P. ovale*.

Barber (1948) concludes that *P. ovale* is the cause of simple dandruff and also says that dandruff is very rare before the age of 9–10. He believes that circulating androgen is necessary for the active growth of *P. ovale* and that oestrogen inhibits its growth. He also states that the administration of oestrogen to males with acne causes cessation of dandruff and diminution of seborrhoea, and that the local application of oestrogen diminishes dandruff. From these observations one assumes that Barber regards androgen and oestrogen as having a direct stimulating or inhibiting action on the growth of *P. ovale*. Unfortunately he is not precise on this point, as, after outlining Darier's views on kerose, he considers that many of the complications of this state, such as acne and increased sebaceous secretion and pityriasis capitis, are a direct androgen effect without the need for any organism such as *P. ovale* to cause the increased desquamation from the scalp. Again one does not know whether any of these views are supported by crucial experiments. Eller and Eller (1949) were unable to detect any changes in the skin of normal young women or in men after the inunction of oestrogen ointment, but they did not carry out their experiments on the scalp. If oestrogen has a direct inhibiting action on *P. ovale* one would expect that the organism would be absent during pregnancy. That this is not the case is shown under Survey 3 below.

Survey 1

Examination was made of scrapings taken from 200 normal scalps selected in such a way that the scalps were devoid of any active lesion or inflammatory condition other than dandruff or sebaceous secretion. Also, apart from diffuse thinning or male-pattern baldness of the hair, no abnormality of the hair was included in the series. The sexes were represented equally and were divided into ten-year age groups, from 0–9 to 80+ years. Each of the first eight groups contained 12 cases of each sex; the last group had four of each sex.



Method. — The scalps were examined and the presence or absence of dandruff was noted, as was the state of the hair, degree of hair loss, and degree of seborrhoea. With a small Meibomian scoop scrapings were taken from six different areas of the scalp radiating in linear fashion from the vertex. The material collected was placed on a slide, mixed with 90% alcohol to facilitate spreading, heat-fixed, stained with methylene blue, and examined microscopically with the 1/12-in. objective lens. The slides were examined for the presence of *P. ovale*, and, depending on the numbers present, the findings were classified as follows:

P.O.– : After an extensive survey of many fields the organism was not seen.

P.O. scanty: The organism was found in numbers up to about 10 after a prolonged search of the slide.

P.O.+ : The organism was present, a few being seen in most fields examined.

P.O.++ : Present in all fields in numbers up to about 20 in the majority of fields.

P.O.+++ : Present in large numbers in most fields examined.

P.O.++++ : Present in large numbers and clumped together in masses in many of the fields examined.

This classification is admittedly an arbitrary one, depending in some degree on the person examining the slides. Nevertheless it seemed to work, and after a little experience it became a simple matter to assign a case to its proper category. Although this classification was useful when it came to assessing certain individual factors, such as greasiness of the scalp correlated with the number of organisms present, it was found simpler to group together the first three subdivisions as category A and the second three as category B for the purposes of recording the overall results.

The dandruff findings were recorded as follows:

D– : No scaling or flaking seen on any part of the scalp.

D slight: Fine white powdery scaling seen in a few areas on the scalp.

D+: White powdery scaling seen with ease, but not in large quantities.

D++: Large amounts of scaling and flaking present, with, in some cases, adherent greasy scaling over much of the scalp.

Results.—*P. ovale* was absent or scanty in 12% of cases—14 male and 10 female. Dandruff was absent or slight in 56.5% of cases—67 male and 46 female. Of these, 48 male and 33 female cases came into category B when the dandruff findings were correlated with those of *P. ovale*. Nine male and nine female cases with the finding "dandruff +/++" came into category A for the *P. ovale* result. Thirty cases showed "seborrhoea" of the scalp. Of these, all except one had infection with *P. ovale* in the range of category B, and nine of these showed the organism clumped in large masses (P.O.++++). Some degree of hair loss, ranging from diffuse thinning to severe Hippocratic baldness, was seen in 49 cases: 38 of them fell into category B for the *P. ovale* finding. The results when divided up into age groups were as follows:

0–9 years	..	P.O.	Category	B	33·3%	Dandruff	+/++	16·5%	of	cases
10–19 "	..	"	"	"	83·0%	"	"	58·3%	"	"
20–29 "	..	"	"	"	71·0%	"	"	46·6%	"	"
30–39 "	..	"	"	"	83·0%	"	"	50·0%	"	"
40–49 "	..	"	"	"	87·5%	"	"	50·0%	"	"
50–59 "	..	"	"	"	79·0%	"	"	41·5%	"	"
60–69 "	..	"	"	"	82·0%	"	"	37·5%	"	"
70+ "	..	"	"	"	72·0%	"	"	47·0%	"	"

These results may conveniently be plotted as a graph, as shown on the previous page.

Survey 2

It is known that *P. ovale* is a lipophilic organism, and during the course of the first survey of scalps it soon became clear that those cases having oily or greasy scalps would show the organism in abundance. In short, it seemed that the presence of sebaceous secretion was the ideal basis on which the organism could flourish. In order to make this point more evident scrapings were taken from the nose and naso-labial folds and from the eyelids of 20 patients. The skin of the nose is rich in sebaceous glands and secretion, whereas the eyelids appear to remain comparatively free from grease. The two areas are contiguous, so it would be perfectly possible for the organism to spread from one site to the other or be transferred by the fingers of the individual or by washing.

Results.—(1) Nasal scrapings gave the following results: P.O. +, 9; P.O. ++, 9; P.O. +++, 2. In all these cases the organism was found without much difficulty. (2) Eyelid scrapings gave the following results: P.O. −, 3; P.O. very scanty, 13; P.O. +, 3; P.O. ++, 1. In 16 cases (80%) the organism was not found or only found with considerable difficulty after a prolonged search of the slide.

Survey 3

As mentioned earlier in this paper, it has been suggested that under the influence of oestrogenic stimulation the infection of the scalp with *P. ovale* diminished. That there was no significant difference between the degree of infection in male and female cases in the first survey would seem to disprove this thesis, but in order to attempt to settle the matter examination was made of the scalps of 32 pregnant women attending an antenatal clinic, their ages ranging between 17 and 42 years.

Results.—(1) *P. ovale* was present in all cases, and, except for two who showed P.O. +, all the cases came into category B. (2) Dandruff was absent or slight in 19 cases and +/++ with some degree of seborrhoea in 13. (3) If these cases are grouped into age groups 17–29 and 30–43, and compared with non-pregnant women in the first survey of similar ages, the following results are obtained:

P.O. Category B:	Pregnant cases, aged 17–29	..	22	out of	23	(96%)
" " "	Non-pregnant cases, aged 17–29	..	12	"	"	16	(75%)
" " "	Pregnant cases, aged 30–43	..	8	"	"	9	(89%)
" " "	Non-pregnant cases, aged 30–43	..	17	"	"	18	(94%)

Thus, so far as the first of these age groups is concerned, there seems to be a definite increase of infection in the pregnant cases; and in the second group the difference is not sufficiently great to be of significance. Certainly there is nothing in these results to suggest that increase of circulating oestrogen diminishes the degree of *P. ovale* infection. The great majority of these women were in the last trimester of pregnancy, when the quantity of oestrogen would have been at its highest and when the stimulation would have lasted for not less than six months. I conclude, therefore, that circulating oestrogen plays no part in determining the degree of infection of the scalp with *P. ovale*.

Survey 4

It has already been suggested that *P. ovale* thrives best in a medium containing sebaceous secretion. This supposition is given support by the findings in nine cases of tinea amiantacea. All these cases showed a dry silvery scaling of the scalp, fine and adherent, in some cases covering most of the hair-bearing area, in others more patchy in distribution. In addition, some cases showed flexural lesions of the seborrhoeic type. *P. ovale* was not found in two cases, was found with difficulty in very small numbers in six, and was classified as P.O. + in the remaining case. It would seem that the excessive dryness of the scalp was a factor responsible for the very low degree of infection with the organism. In parenthesis it should be said that I would agree whole-heartedly with the thesis put forward by Brown (1948) that the disease is due to underlying emotional factors, and I would prefer the title of "neurodermatitis of the scalp" to the outmoded one of tinea amiantacea.

Survey 5

During the course of these investigations 17 cases of psoriasis of the scalp were seen and scrapings taken.

Results.—*P. ovale* was absent in 11 cases, scanty in one case, + in three cases, and +++ in two. Of these last two, one had a very greasy scalp and the other had such a slight degree of scaling that it could be differentiated from ordinary dandruff with some difficulty. In the main, the scalps examined were dry and the scrapings were taken from the centres of obvious and well-demarcated patches of psoriasis. Once again it seemed that the dryness of the lesion and the absence of sebum was the cause of the slight degree of infection with *P. ovale*.

Survey 6

In the past, claims have been made that inoculation of the skin with cultures of *P. ovale* would produce lesions of seborrhoeic eczema. As has already been indicated, the methods used are open to criticism, and conflicting results have been obtained when scrapings from "seborrhoeic" lesions have been examined for the presence of the organism.

In the course of this investigation 16 cases were diagnosed as suffering from seborrhoeic eczema. Eight cases showed generalized flexural lesions involving the scalp, ears, neck, axillae, breasts, umbilicus, perineum, and intergluteal fold. In six scalp scrapings *P. ovale* was absent or scanty in five and + in one. In 20 scrapings from behind the ears and other body areas mentioned, the organism was scanty in one retro-aural scraping and absent in all the others, although a monilia-like organism was present in one specimen taken from an intergluteal lesion. Scrapings taken from four cases of pityriasis circinata of the chest showed the organism to be absent in three cases and scanty in one. In four cases having seborrhoeic eczema of the ears and scalp five scrapings were taken—one showing P.O. ++, one scanty P.O., and three negative.

From the findings in the admittedly rather small number of cases one would not deduce that *P. ovale* was the cause of the disease. Unless secondary infection was present—and cultures invariably produced a pure growth of coagulase-positive *Staphylococcus aureus*—the lesions were red, scaly, and remarkably dry, an observation much in keeping with that of Percival (1936), who comments on the lack of seborrhoea in cases of seborrhoeic eczema.

Discussion

It has been the aim of this investigation to support the thesis that *P. ovale* has nothing to do with the cause of dandruff, seborrhoea, or seborrhoeic eczema. In consequence I would strongly support the conclusions reached by Martin-Scott (1952), which were backed by cultural and inoculation studies.

In the first survey of 200 "normal" scalps one of the most striking findings was the sharp rise in the incidence of dandruff and degree of *P. ovale* infection at puberty. Another point of interest was the greater degree of dandruff and slightly larger number of heavy *P. ovale* infections in the female than in the male. The sudden increases of dandruff and heavy *P. ovale* infection at puberty might lead one to suppose that the two conditions are causally associated, but other factors must be considered, notably the increase of sebaceous activity at that age.

It was noted that of 30 cases with "seborrhoea" of the scalp all except one showed a heavy *P. ovale* infection, and that 38 out of 49 cases with some degree of hair loss showed the same finding. Sabouraud thought that increased sebaceous secretion led to hair loss, and more recently Flesch (1951) has shown that squalene, a normal constituent of sebum, will cause loss of hair when applied to the skin of rabbits. In short, it seems that it is the heavy sebaceous secretion which permits *P. ovale* to flourish in these cases—a reasonable conclusion, as the organism is very lipophilic. The later surveys of nose and eyelids and of various dry scaly conditions of the scalp and body all tend to support this view, and in consequence the increased infection at puberty is to be expected owing to the increased greasiness of the skin at that time.

For additional proof that *P. ovale* does not cause dandruff I would point to the 48 males and 33 females who showed slight or no dandruff in the presence of heavy *P. ovale* infection. In addition it was possible to find comparable degrees of infection on the skin of the nose without any sign of scaling or abnormality of the surface.

This, of course, does not lead us any nearer to understanding the precise cause of dandruff, but I would suggest that it is the normal desquamation of the scalp, similar in every respect to the "invisible" scaling on other parts of the skin caused by the normal replacement of cornified cells. The difference lies in the retention of the scales by the hair of the scalp—a suggestion which might seem to derive support from the shorter hair and more frequent scalp-washing in the male, who shows a lower incidence of heavy dandruff when compared with the long-haired female, whose scalp is washed less often lest her "waves" should cease to remain permanent.

The suggestion that androgen increases and oestrogen decreases the degree of dandruff would seem to be unsupported by the findings in the 32 pregnant cases, and also by the greater incidence in the female than in the male. Nevertheless it is difficult to resist the conclusion that endocrine factors must have something to do with the sharp increase at puberty, although I would not agree with Barber's statement that dandruff is rare before the age of 9–10.

This paper, it must be admitted, is largely iconoclastic and offers little constructive suggestion to explain some of the conditions described. However, to attempt to explain the causes of seborrhoeic eczema and neurodermatitis of the scalp would take me far beyond the scope of this investigation, as many factors other than the bacteriology of the scalp would need to be considered. Nevertheless it is hoped that *P. ovale* will no longer be regarded as the major or only cause of the conditions discussed, and, although many of the findings are of a negative type, I have yet to read of any convincing evidence in the shape of inoculation studies which would support the thesis that *P. ovale* is the cause of dandruff or seborrhoeic eczema.

Summary

Some of the problems concerning the relationship of *Pityrosporum ovale* to dandruff and other "seborrhoeic" conditions of the scalp and body are discussed and the literature on the subject is briefly reviewed.

Examination was made of 200 normal scalps and the degree of infection with *P. ovale* was correlated with the degree of dandruff present. From the findings it was considered that there was no evidence to justify the theory that *P. ovale* caused the dandruff. Instead it was suggested that the degree of infection was influenced by the quantity of sebaceous secretion, and that the increased flow of sebum at puberty would explain the rise in the incidence of infection at that age. It was also noted that the amount of dandruff was heavier in the female than in the male.

The suggestion that sebaceous secretion was the main factor influencing the degree of infection with *P. ovale* was supported by the findings in scrapings taken from the skin of the nose when compared with scrapings from eyelids in 20 cases. Further support was given by the findings in nine cases of tinea amiantacea, 17 cases of psoriasis of the scalp, and 16 cases of seborrhoeic eczema of the scalp and trunk. In most of these dry scaly conditions the organism was absent or was found only in small numbers.

The suggestion that oestrogens diminish the degree of dandruff and *P. ovale* infection receives no support from the findings in the 100 male and 100 female normal scalp scrapings. Examination of the scalps of 32 pregnant women, most of whom were in the last trimester, showed a rather greater degree of infection when compared with non-pregnant women of the same age groups.

It is concluded that *P. ovale* is not the cause of dandruff but is a harmless organism on the scalp which thrives best in the medium provided by a heavy flow of sebum.

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The county health department of Cheshire has performed a useful service in publishing *A Cheshire Index*, a booklet listing in alphabetical order and in five sections (*a*) the county districts and civil parishes, (*b*) civil parishes with place-names therein, (*c*) place-names of the administrative county, (*d*) county boroughs and place-names therein, and (*e*) place-names outside Cheshire with a Cheshire postal address. In a modestly worded preface the department invites the correction of any error of omission or insertion. Similar lists of the place-names of the other counties in the United Kingdom would be a boon to all those who have to verify the names of villages, hamlets, and district localities in larger towns.

A CASE OF PRIMARY OVARIAN PREGNANCY

BY

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Primary ovarian pregnancy is an obstetrical rarity. Courtiss (1942) gave its incidence as 1 in 25,000 pregnancies and, using the figures of the Mayo Clinic, stated that it occurred in about 0.5% of ectopic pregnancies. Eckerson (1941), basing his estimate on the statistics of St. Luke's Hospital, reckoned that it occurred in something like 0.2% of ectopic gestations. Just over 100 cases have been reported in the English language, and a perusal of the relevant British, American, and Dominion obstetrical and gynaecological references leaves one with the impression that some of these may be spurious, as they seem to be backed by inadequate information.

Spiegelberg (1878) established four criteria upon which the diagnosis is to be based. He stated that if a case is to be accepted as one of primary ovarian pregnancy: (1) the Fallopian tube on the affected side must be intact and separate from the ovary; (2) the gestation sac must occupy the position of the ovary; (3) the gestation sac must be connected to the uterus by the ovarian ligament; and (4) ovarian tissue must be found in the wall of the sac. Since the following case seems to comply with these standards, it is submitted as an addition to the existing literature on the subject.

Case Record

A woman aged 37 was admitted on August 13, 1951, complaining of dull aching left-sided pain of some hours' duration. A similar but less severe attack had occurred one week previously, but had passed off in a few hours. Both attacks had been accompanied by nausea and retching, but there was no vomiting. The pain did not radiate and was not aggravated by movement. The last menstrual period had started on June 29.

The patient had been married for 17 years, but had never been pregnant. In 1942 she and her husband had undergone a series of investigations by a "specialist" in infertility. The scope and nature of these investigations were not clearly revealed by the patient, but she was emphatic in stating that no apparent cause for her failure to conceive had been advanced.

At the time of her admission she had been attending regularly at the out-patient department of the Maudsley Hospital, where she was being treated for what she called "nerves." Her history was otherwise without significance.

Examination showed that the patient's general physical condition was good. Her pulse rate was 80 a minute, regular, and of good volume. Her blood pressure was 105/65 mm. Hg. Examination of the cardiovascular and respiratory systems revealed no abnormality. The abdomen moved freely with respiration and there was no rigidity. Some guarding was noted in the left iliac fossa, where tenderness was elicited on deep palpation. No mass was, however, felt by the examining hand. On bimanual examination the uterus was found to be normal in size and consistence and to be acutely anteflexed. No palpable mass could be detected, but tenderness was very acute in the left fornix. A presumptive diagnosis of ectopic pregnancy was made and the patient prepared for laparotomy. Two pints (1.1 litres) of cross-matched blood of the appropriate group was held in readiness.

Operation.—Under thiopentone, nitrous oxide, oxygen, and cyclopropane anaesthesia the abdomen was opened through a subumbilical midline incision. The uterus was found to be normal in size and to occupy the position disclosed by vaginal examination. A few tenuous adhesions were found on the posterior uterine wall, but no evidence of gross inflammation or of endometriosis was detected. The right tube and ovary were normal in appearance, as was the left tube. At the site of the left ovary was a tumour, about 2½ cm. in diameter, which appeared to consist of the ovary in addition to an adherent mass of blood clot. There was no free haemorrhage in the peritoneal cavity. Left oophorectomy was performed and the specimen submitted to the pathologist, Dr. J. H. H. Keale, for histological examination. The abdomen was closed in the usual manner, and the patient made an uninterrupted recovery, being discharged from hospital 14 days later.

Ovarian mass split to reveal gestation sac of very early foetus.

Pathological Report.—Microscopical examination of the tissue was performed by Dr. Keale, who reported: "A fibrocystic ovary to which was attached a circular mass of tissue fully 2 cm. in diameter containing a small ragged haemorrhage. Contained in the haemorrhage and lying centrally was a small mass of tissue which was considered to be a very early foetus. A section of this circular mass of tissue showed fibrous tissue, and on the inner edge was a haemorrhage with chorionic villi. A section of the ovary proper displayed a few follicular cysts only." The pathologist concluded that the specimen submitted was "an ovarian pregnancy."

The normal appearance of the left tube, the location of the foetal sac at the site of the left ovary, the fact that the mass was connected to the uterus by the ovarian ligament, and the presence of chorionic villi situated in close relation to ovarian tissue, mark this case as satisfying Spiegelberg's criteria and enable one to classify it as a case of primary ovarian pregnancy.

Discussion

The cause of primary ovarian pregnancy has evoked much speculation, but little that is definite is known concerning it. As recently as 1888 Lawson Tait gave it as his opinion that no such condition existed. When, however, irrefutable evidence to the contrary was repeatedly submitted, challenging medical opinion to explain this phenomenon, endometriosis of the ovary was initially invoked as a convenient and plausible basic cause. In the above case (as in many other cases in the literature) there was no evidence of endometriosis on naked-eye examination of the pelvis, and histological examination of the ovary revealed neither endometriosis nor decidual reaction to implantation.

It is known that fertilization and implantation may occur initially in the Fallopian tube, and that the foetal sac subsequently becomes dislodged, to achieve a secondary implantation in the ovary (secondary ovarian pregnancy). It is possible also that even when the tube on the affected side presents a normal appearance it nevertheless is the primary site of implantation in certain cases hitherto classified as primary ovarian pregnancies. Not all cases can, however, be explained away in this fashion, as fastidious

histologists have in many instances subjected the apparently normal tube on the affected side to serial histological examinations and in the end have been compelled to concede it normal upon the basis of a complete absence of chorionic tissue.

Curtis (1941) suggested that in certain cases the ovum, after becoming fertilized in the Fallopian tube, may "slide downwards to the gaping recently ruptured ovary, there to develop." Other writers, like Mann *et al.* (1941) believe that, "the ovum becomes fertilized while remaining in the follicle and develops its sac from contiguous ovarian tissue." Each of these views has the merit of plausibility, and it is not improbable that both processes may occur.

In view of the unfavourable nature of the implantation site it might be supposed that ovarian pregnancies generally would come to an abrupt and early termination. Statistics, however, do not support this view, and Dale (1947) collected from the literature 38 cases in which the pregnancy had proceeded beyond seven months, and from which 12 living infants had been produced.

Lithopaedion formation has been recorded in several cases of ovarian pregnancy, and De Lee (1943) reports an ovarian hydatidiform mole. The coincidence of ovarian pregnancy and eclampsia reported by Pride and Rucker (1942) may, however, claim distinction as a rarity of rarities.

Many writers have stressed the relatively slight danger of alarming haemorrhage in ovarian pregnancy as compared with the tubal variety, and the above case in this respect conforms to type. Indeed, it stands out in my experience as one of the very few cases of ectopic pregnancy in which the administration of a blood transfusion would have been completely without justification.

Summary

The relative rarity of primary ovarian pregnancy is stated, with statistical support.

Spiegelberg's criteria of primary ovarian pregnancy are quoted and a case is reported which seems to satisfy these criteria.

Various views on the aetiology of primary ovarian pregnancy are mentioned, with brief comment.

The unexpectedly high proportion of viable infants resulting from ovarian pregnancy is mentioned.

The relative infrequency of severe haemorrhage attendant upon this type of ectopic gestation as compared with tubal pregnancy is stressed.

I am indebted to Mr. Douglas M. Lindsay for permission to report this case, which occurred in his unit at Beckenham Hospital.

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DELAYED CHLOROFORM POISONING IN OBSTETRIC PRACTICE

BY

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Cases of delayed chloroform poisoning in obstetric practice have been reported by numerous writers. The outcome in many of the cases was fatal. Nine of the 10 cases reviewed by Gibberd (1935) were fatal. Stander (1932) reports a mortality of 80% in five cases. This figure is regarded as too pessimistic by Sheehan (1940), since his last six cases recovered and two of them were very severe. Clinical histories of three patients who developed delayed chloroform poisoning are here briefly described.

Case 1

The patient, aged 24, was admitted to hospital on January 10, 1947, following a difficult forceps extraction under chloroform anaesthesia at home 48 hours previously. This was her first confinement and followed a normal antenatal period. The duration of labour was 83 hours. The food and fluid intake had been insufficient during this time, and the patient had experienced troublesome vomiting.

On admission she was drowsy and slightly jaundiced. There was no vomiting. Her blood pressure was 130/85 and her temperature 99.8° F. (37.7° C.). Prophylactic penicillin had been given since delivery. There was no liver tenderness or enlargement. Shortly after admission she became very restless and cried out as if in pain. This was associated with muscle-twitching. Periods of extreme restlessness occurred during the next three days, and on occasion she became almost maniacal. The jaundice deepened during this time. No vomiting occurred and sips of fluid were taken. Her condition then gradually improved, and a slow, steady recovery was made.

Retention of urine before and after admission into hospital necessitated catheterization. The urine output was always satisfactory. A bacteriological examination of the urine showed a *Bact. coli* infection, and the cervical swab yielded a growth of haemolytic streptococci. The blood culture was negative. Pyrexia persisted for several days after admission, but responded to penicillin and sulphonamide therapy.

Intravenous dextrose therapy was given on admission and continued for five days. In each 24 hours two litres of 5% dextrose and one litre of 4.3% dextrose in 0.18% sodium chloride were given. Five units of soluble insulin twice a day, 20 ml. of 10% calcium gluconate intravenously, and vitamin B by injections were given each day. Intramuscular paraldehyde was administered when necessary to control the restlessness.

Laboratory Investigations.—On January 11 (third day after delivery) an immediate positive van den Bergh reaction was given by the serum. The indirect van den Bergh reaction was 5.8 units; this increased to a maximum of 10.3 units on January 13. The alkaline phosphatase was 21.4 King–Armstrong units on January 11 and 22.3 on the 15th; it then slowly returned to a normal level. At all times the colloidal gold test showed no precipitation (0). The Takata–Ara reaction did not show a positive result, and the serum thymol turbidity varied between 0 and 3.2 units. Other blood chemistry estimations on January 11 showed the alkali reserve 34 vols. CO_2 per 100 ml., with the chlorides and total protein within normal limits. The blood urea was 108 mg. per 100 ml., and remained raised for several days. On January 15 the blood urea was 104 mg. per 100 ml., and then returned to a normal level. The urine contained bilirubin and urobilin. The Rothera test was negative on all occasions before and after the beginning of intravenous dextrose therapy. The blood-sugar level of 135 mg. per 100 ml. of blood on January 13 was probably influenced by the dextrose therapy.

Case 2

A primigravida aged 23 started in labour on April 29, 1951. Prior to this the pregnancy had been normal. Further details regarding her labour and delivery were obtained from her doctor. A manual rotation and forceps extraction for a right occipito-posterior presentation after 28 hours' labour had been carried out under chloroform anaesthesia, the duration of which was approximately 20 minutes. Two hours later chloroform anaesthesia was again used for manual removal of the placenta. The history did not indicate any vomiting or undue maternal fatigue before delivery. Vomiting occurred only once after the second anaesthesia. Jaundice appeared about 24 hours after the forceps extraction, increased for two days, and then gradually faded. The patient did not have any symptoms other than nausea and general weakness. She was able to take light diet from the time of delivery, and liberal glucose drinks were given.

She was admitted into hospital on May 10. On examination the skin showed slight icterus, but otherwise her condition was satisfactory. Prophylactic penicillin had been given throughout the lying-in period. Pyrexia had not occurred. Complete recovery was made in hospital without any special treatment. There were no relevant laboratory investigations to report.

Case 3

A primigravida aged 35, following a normal antenatal period, had her confinement at home under the care of her own doctor. On September 3, 1951, after 36 hours' labour, twin males were delivered, the first by a forceps extraction and the second by breech extraction. The patient was under chloroform anaesthesia for approximately 25 minutes. Four and a quarter hours later, chloroform was again administered, and manual removal of the placenta was performed. Adequate sedation was given prior to delivery and only slight post-anaesthetic vomiting occurred. Jaundice developed on the second day after delivery. The patient was sent into hospital on September 7.

On admission she was semi-comatose and deeply jaundiced. There was abdominal tenderness over the liver area, but no liver enlargement was detected. The blood pressure was 130/95 and the temperature 98.4° F. (36.9° C.). Slight oedema of the legs was present. The patient remained comatose for 24 hours. Hiccup was troublesome. During the next four days slight improvement took place, but there was extreme drowsiness, with mental confusion and periods of restlessness. No vomiting occurred and the swallowing reflex was present, enabling small quantities of fluid to be taken by mouth. The urine output was satisfactory, but catheterization was necessary for several days owing to retention. Five days after admission a rigor occurred, due to a *Bact. coli* urinary infection, which responded to streptomycin therapy.

Treatment in this case followed similar lines to that in Case 1. Intravenous dextrose and saline therapy was continued for four days after admission. A slow but steady recovery was made.

Laboratory Investigations.—On September 7 (fourth day after delivery) blood chemistry estimations showed: alkali reserve, 54 vols. CO_2 per 100 ml.; chlorides, 570 mg. per 100 ml.; total protein, 5.3%; blood urea, 50 mg. per 100 ml.; and sugar 52 mg. per 100 ml. On September 8 the alkali reserve was 45 vols. CO_2 per 100 ml.; blood urea, 24 mg. per 100 ml.; and blood sugar, 120 mg. per 100 ml. Thereafter the above estimations were within normal limits.

On September 7 the direct van den Bergh reaction was positive, and the indirect reaction 14.7 units. The alkaline phosphatase was 21.2 King–Armstrong units, serum thymol turbidity 2.2 units, and the thymol flocculation positive. The colloidal gold test showed no precipitation (0). On admission the urine contained a trace of albumin, bilirubin, and excess urobilin. The Rothera test was negative on all occasions.

Comment

Only in Case 1 had the labour produced notable maternal fatigue and been accompanied by much vomiting before delivery. Exhaustion due to a long labour, starvation with dehydration from vomiting, and poor food intake, and also sepsis, are considered by Sheehan (1940) to be the most important factors predisposing to possible poisoning when chloroform anaesthesia is used. Uterine sepsis was present in Case 1. The urinary infections in Cases 1 and 3 occurred after the appearance of the jaundice.

Chloroform is favoured in domiciliary practice, since by its use induction of anaesthesia is easy and rapid; also, by reason of its safety, in rooms where open fires are present. Stander (1932) states that if chloroform is used it should be given in very small quantities for the "crowning" of the head, and at other times it should be avoided if some other anaesthetic is available. There is no doubt that great caution is necessary in using it, and that it is contraindicated in labour cases in which exhaustion is evident, owing to the factors previously mentioned, or in which there is a history of toxaemia.

When delayed chloroform poisoning occurs it may follow one induction or two inductions separated by a short interval of time, as in Cases 2 and 3. Kerr and Moir (1949) point out the danger of repeated administration of choloroform at short intervals of time or for longer than 15 minutes at one time. The total amount of anaesthetic used varies very much in every case, and usually the exact quantity is not known. In cases in which two inductions are given, it is probably the total quantity of anaesthetic administered that is the important factor, rather than the fact that the anaesthetic has been given in repeated doses.

The cases reported all conformed to the usual clinical picture found in cases of delayed chloroform poisoning. The jaundice appeared during the two days after the administration of the anaesthetic, vomiting being followed by drowsiness, restlessness, and perhaps coma. Vomiting did not occur in the cases above, but in those reviewed by Gibberd (1935) vomiting was the first symptom in most cases.

The liver tests performed in Cases 1 and 3 indicated some degree of liver derangement. Such tests, however, as is well known, give very variable results, and may show no change even when the liver damage is severe. Again, in Case 1 the alkali reserve was found to be low and the blood urea raised during the worst phase of the illness. There was less disturbance of these values in Case 3. If liver damage is extremely severe the blood urea may not increase, but in some fatal cases very high levels have been reported, as in a case recorded by Gibberd in which the blood urea reached 300 mg. per 100 ml.

Summary

Three cases of delayed chloroform poisoning in obstetric practice are recorded. All the patients recovered.

Stress is laid on the danger of chloroform anaesthesia when used in certain types of obstetric cases, particularly when there has been a long labour associated with dehydration and starvation acidosis.

A brief account of the treatment given in these cases is described. The early administration of intravenous dextrose was carried out.

I would like to express my thanks to Mr. F. E. Wheeler, under whose care these patients were admitted, and to Dr. J. Mills, in whose department at the Royal Berkshire Hospital, Reading, the pathological investigations were carried out.

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Medical Memorandum

A Case of Puerperal Tetanus of Unusual Origin

The occurrence of acute intestinal obstruction as a complication of pregnancy is fortunately an uncommon incident. Interest is added to the account of this case by the fact that the patient later developed tetanus.

CASE REPORT

The patient, a 25-year-old married woman, was admitted to hospital on November 4, 1949, at about 6 p.m., complaining of vomiting and abdominal pain. She had been delivered of a live male child weighing 6 lb. 9 oz. (3 kg.) at 4 a.m.—that is, 14 hours before admission.

The history was that abdominal pain started on October 30, and this had been accompanied by some vomiting. She had not called her doctor until the next day. It was presumed that she was beginning labour, and as it was her first pregnancy she was treated at home for the next 48 hours. She was admitted to a maternity hospital on November 2 because her condition was not satisfactory. She was vomiting and her whole abdomen was tense and tender. The diagnosis was uncertain, but she was treated with intravenous fluids and gastric suction. In the early hours of November 4 she was delivered by forceps. She was transferred to the general surgical hospital because delivery had not caused any cessation of the vomiting and her abdomen was still distended and painful. Her bowels had not been opened since November 2, but enemata had produced some flatus.

On admission her colour was poor, and her pulse weak and rapid at 116 a minute. Her tongue was dirty, and her respirations were shallow. Her abdomen was distended, and there was generalized tenderness with muscular guarding. On auscultation it was silent. Her blood pressure was 110/80. Rectal examination showed an absence of faecal material, and there was tenderness. She vomited some brown-stained fluid which was not faecal-smelling. A diagnosis of peritonitis with paralytic ileus was made.

Gastric suction and intravenous therapy were begun and "omnopon," ¼ gr. (22 mg.), was injected intramuscularly. With this treatment her general condition improved and the continuous gastric aspiration produced much brown fluid. She continued to progress favourably for about 10 hours, but then deterioration began. Operation was decided upon at this stage because, although the cause of the peritonitis was not known, it was obvious that surgical intervention was required. In addition to the above treatment she was given soluble penicillin, 500,000 units as an initial dose, followed by 100,000 units four-hourly intramuscularly.

Operation.—This was performed by Mr. R. G. Paul at 2 p.m. on November 5. When the peritoneal cavity was opened it was found to contain a large volume of purulent sanguineous fluid. There was gross distension of the small bowel to a point about 3 feet (0.9 metre) proximal to the ileo-caecal valve. At this site the ileum was constricted by a band running from the brim of the pelvis on the right side to the posterior abdominal wall in the paracolic region. Beyond the band the ileum was gangrenous, being friable and greenish grey in colour. The caecum and the rest of the colon were inflamed and collapsed. The uterus and Fallopian tubes showed evidence of external inflammation only. The band was divided. The gangrenous portion of the terminal ileum, which stretched to the ileo-caecal valve, together with about 12 in. (30 cm.) of intestine proximal to the point of constriction, was rapidly excised. As the patient's condition was not improving and was likely to deteriorate very rapidly, Paul's tubes were tied into the ileum and the caecum. Both ends were brought out through the right paramedian incision and the wound was closed in the usual manner. At the end of the operation the patient's condition was critical.

During the next 48 hours she remained seriously ill, but continuous gastric suction and intravenous therapy kept the condition under control. Soluble sulphadimidine, 1 g. four-hourly, was given in the intravenous drip. Her pain was alleviated by pethidine.

On November 10 she was progressing satisfactorily, but at 9 p.m. she complained of stiffness of her jaw and became restless and worried. She settled down when she was given phenobarbitone, 1½ gr. (0.1 g.), and paraldehyde, 4 ml. intramuscularly. At 2 a.m. on the 11th a note was made that the patient was overbreathing and distressed because of spasms of her jaw. A diagnosis of tetany due to hyperventilation was made, and 10 ml. of 10% calcium gluconate was given intravenously, and 4 ml. of paraldehyde intramuscularly. At 9 a.m. her general condition was worsening and the trismus was established. Diagnosis of tetanus was made. Rectal paraldehyde, 6 dr. (23.5 g.) in 6 oz. (170 ml.) of saline, was given. Antitetanic serum, 100,000 units, was administered intramuscularly. At 11.30 a.m. a general spasm occurred. Circulatory failure became evident at once and the patient became unconscious and cyanosed. Despite cardiac stimulants and other resuscitatory measures death occurred at 12.50 p.m.

Necropsy.—This did not reveal any abscess formation in either the wound or the abdominal cavity. The uterus and Fallopian tubes showed evidence of inflammation on their peritoneal surfaces only. Swabs were taken. Direct examination did not reveal *Clostridium tetani*, but culture of the pus from the superficial part of the abdominal wound showed these organisms.

COMMENT

The diagnosis of intestinal obstruction is not easy, especially at term. The time in pregnancy at which obstruction is likely to occur is given by Matthews and Mitchell (1948). The danger periods are (*a*) during the fourth to fifth month, when the uterus ascends from the pelvis; (*b*) during the eighth to ninth month, when the foetal head descends into the pelvis; and (*c*) during delivery and the early puerperium, when there is a pronounced change in the size of the uterus.

With regard to the intestinal obstruction, there are three points to be emphasized. First, one of the causes of the delay in diagnosis is the fact that the contraction of the abdominal wall which accompanies the intestinal colic obscures the uterus and can be interpreted as being due to, or in fact, uterine contractions. Secondly, when the diagnosis is made laparotomy should not be delayed unless labour is either in progress or imminent. Thirdly, gastric suction and intravenous therapy must not be used as a substitute for surgery. Their institution always causes improvement even though the obstruction is still present and the vitality of the bowel is being further impaired. Persistent pain and abdominal tenderness, especially when it is localized, after decompression of the bowel is always of serious import and calls for early surgical intervention.

Cases of tetanus still occur in this country. Sevitt (1949) discussed two recent cases. The above case, however, reminds us that the organism is present in the bowel. Giuseppe Spadaro (1948) collected 42 cases in the world literature and added five due to operations on the abdominal portion of the digestive tract. The normal bowel wall is a barrier to the passage of organisms, but when its vitality is impaired then penetration can occur. In cases in which the bowel is so damaged antitoxin might justifiably be used.

The delay in the diagnosis of tetanus, which may be vital, is due to the fact that the condition is so rare that early signs are either missed or misinterpreted because the disease is not considered.

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Reviews

BRONCHOSCOPY AND OESOPHAGOSCOPY

Bronchoesophagology. By Chevalier Jackson, M.D., and Chevalier L. Jackson, M.D. (Pp. 366; 263 illustrations. £3 3s.) Philadelphia and London: W. B. Saunders Company. 1950.

This is a fourth edition, considerably revised and under a new title, of a well-known and very successful book. It is based, essentially, on the fundamental work of Chevalier Jackson senior, whose name will always be associated with the development, organization, and establishment of safe bronchoscopic and oesophagoscopic methods. As a pioneer in this field he is unequalled. His son and co-author carries on his father's good work. The horrid title is defended by the explanation that the book sets out to do more than present the bare bones of endoscopy and tries to give the whole picture of the diseases of the bronchi and oesophagus.

The most important part of the book is the presentation of technical methods. The Philadelphia school of endoscopists, led and inspired by Chevalier Jackson, have justly achieved a world-wide reputation for their efficiency, skill, and dexterity. Your reviewer was privileged, 22 years ago, to work at the Chevalier Jackson Clinic at Jefferson Hospital under the tutelage of Dr. L. H. Clerf, and will be ever grateful for the kindness and proud of the splendid training received. A lasting knowledge can be rapidly obtained when one is taking part in some 100 examinations a week. The memory is still vivid of the effortless and rapid dexterity of technique, especially in removal of foreign bodies. Objects that had perhaps already defeated several attempts at removal elsewhere would be extracted in some two minutes by the stop-watch.

The vast experience of the Philadelphia schools in removing foreign bodies of every conceivable type from the bronchi and oesophagus is unique and probably always will be. In this book the reader can learn from this accumulated experience; he can use it as a textbook or as his reference book when faced with the problem of dealing with a foreign body. An interesting development is the use of the magnet; less attractive is the account of extraction of foreign bodies by external puncture. One wonders also how often the elaborate technique of removing small pins, etc., from peripheral bronchi is really justified. Most of these small foreign bodies are better left alone.

The authors take great care in describing the position of the head and shoulders in introducing the bronchoscope or oesophagoscope, and the necessary alterations during further passage of the instruments. The Jackson contribution in these matters is classic. As my own knowledge rests entirely on what I learnt in Philadelphia I am hesitant about calling attention to the position of the head as depicted diagrammatically in Fig. 30c and other diagrams. It does not seem anatomically possible, if the neck is fully flexed on the trunk, for the head to be hyperextended on the neck. I have always remembered the instruction that for exposure of the larynx the plane of the face should be *parallel to* the plane of the body surface and as much above it as possible. These diagrams showing the head hyperextended will encourage the inexpert operator to try to introduce the bronchoscope with the head thrown back and the neck not flexed on the trunk. It would be an advantage if diagrams such as this were either replaced by or supported by actual photographs. The numerous photographs of the grouping around the patient at endoscopy do not show the head position clearly.

Incidentally, in all the photographs the members of the team wear their mask with the nose uncovered. Quite apart from the risk of contamination from the operator, there is the grave risk of infection of the operating team by the patient. This also should be altered in future editions. Spectacles are recommended, and a nurse to stand by and change the spectacles as they become soiled. The Negus face-shield not only gives much more protection, but also dispenses with the need for a nurse to stand by.

Chevalier Jackson's valuable contribution in describing so clearly the various check-valve actions in bronchial obstructive lesions is well known and is fully explained, but the frequent repetition of description and of diagrams illustrating it becomes rather tedious and might with advantage be lessened. Physicians would do well to pay attention to the counsel: "Every medical student should be taught that no physical examination of the chest is complete without listening at the patient's open mouth for a wheezing sound." This invaluable sign often provides more information and in a much shorter time than can be achieved with percussion and the stethoscope.

The account of lung abscess leaves much to be desired, especially the suggestion that acute post-tonsillectomy lung abscess "is a distinct type." The claims for a high degree of success in bronchoscopic therapy are less enthusiastically pressed than in the past—a change that should meet with general approval. The claims of bronchoscopy in diagnosis and examination are ably set out.

The value of examining aspirated bronchial secretions for malignant cells in the diagnosis of bronchial carcinoma is fully presented, but a notable omission is any reference to Dudgeon's wet-film method, evolved at St. Thomas's Hospital, which forms the basis of this investigation. Surely his contribution should be acknowledged.

In describing the dangers of oesophagoscopy more emphasis should be placed on acute perforation of the oesophagus and the need for prompt thoracotomy and closure of the rent by suture. A special account of this disaster and its management should be given. Too much is said of treatment of residual abscess and too little of immediate recognition of the disaster and its reference to a surgeon; many patients with perforations never live to develop a residual abscess.

These criticisms are not meant to be derogatory and are almost trivial in relation to the vast amount of first-class information clearly and authoritatively presented.

There is, however, one big criticism that must be made; it is not meant to belittle, and in some ways it is embarrassing to make it in view of the ripe experience of and the respect due to a pioneer of the quality of the senior author. It is now well over a quarter of a century since the bronchoscopic and oesophagoscopic technique, as described in this book, was established at Philadelphia. It was a triumph of organization and performance, allowing safety and success to be achieved. Very large numbers of pupils have been taught these methods with great advantage to everyone. Yet there has been almost no significant change in the basic technique and in the instruments used. The elaborate head-holding technique, for instance, is a quite unnecessary waste of man-power, and rather pathetic when one sees it slavishly followed by devotees in many places. It seems to be in danger of becoming a traditional ritual indulged in by the disciples of the Jackson school.

The same criticism applies to the bronchoscopes and oesophagoscopes used. These also have remained unchanged throughout the years, presumably because they are thought to have achieved perfection. The jealous guarding of their design is also fast becoming a tradition, for they have been outdated and outmoded by other instruments just as the motor-cars of the same vintage have been replaced by later and more efficient models. The continued, unquestioned acceptance of these obsolete instruments by the devotees is somewhat remarkable. If this state of affairs continues much longer, the Jackson type of bronchoscope and oesophagoscope will attain a dignity due to custom and usage only comparable to that of a sacramental weapon or staff. Sooner or later the break will have to come unless it is to remain as unchanged as Holy Writ.

The bronchoscopes are very wasteful of space. The wall is unnecessarily thick compared with the lumen, and even the effectiveness of this is further encroached upon by the excessive projection of the light-carrier channel. The lip of the instrument is also too big and clumsy, especially in the smaller sizes, when every fraction of a millimetre counts. The Negus type of instrument, which has been used for

many years in Britain and has almost completely displaced the Jackson instruments, has none of these disadvantages; the size and construction are as economical as possible and give a much more generous view and operating space. The objections to the Jackson type of oesophagoscope are less serious, but the Negus type of instrument is similarly much more efficient.

Your reviewer is anxious to repeat that these criticisms are made only with a full sense of the respect due to the great contributions and pioneer work of the Jackson school and are not meant to be unkind or disparaging. The book itself should be familiar to all those, whether thoracic surgeons or physicians or "bronchoesophagologists," who have to deal with the oesophagus and air passages.

R. C. BROCK.

PRACTICAL DERMATOLOGY

Practical Dermatology for Medical Students and Practitioners. By Professor George M. Lewis, M.D., F.A.C.P. (Pp. 328; 99 plates. £1 17s. 6d.) Philadelphia and London: W. B. Saunders Company. 1952.

This is a simple presentation of dermatology for students and general practitioners. It is an admirable book, easy to read, well produced, and excellently illustrated in black-and-white. With no more than six pages of introduction the author gets into the heart of his subject, discussing with much common sense the various groups of dermatological ills in a manner that any doctor can understand. Though the introduction deals with the special features of dermatology, it is mostly devoted to the taking of an adequate history, performing a thorough physical examination (not limited to the skin), and verifying clinical assessments by laboratory tests.

There is a pleasing and judicious use of heavy type to emphasize the essentials in each paragraph. The balance and proportion of the work are excellent, and there is no section that falls short of this high standard. The presentation of psoriasis and the summary of the problem of eczema are admirable. There is also a section on the acute specific fevers. Only very occasionally is the variation of American from British experience felt, as in the presentation of tuberculosis and erythema nodosum and the scant attention to chilblains. The section on fungous diseases is particularly good and there is here a warning against excessive treatment.

The author is clearly a sound and experienced physician, and there are few criticisms to be made of his work. He does not mention the course and prognosis of dermatitis herpetiformis, the fact that black hairy tongue often results from sucking penicillin lozenges, or that ichthyosis may respond to large doses of vitamin A. The treatment of rosacea is perhaps a little inadequate, but these are small points. How true are such injunctions as that "sympathetic listening, allowing the patient to ventilate his problem, is often an important part of treatment," and that "acne should be taken seriously and the patient treated with sympathy and understanding." In the account of pyodermia there is a warning against the use of antibiotics in a routine fashion; each case should be treated on its merits.

This is a most important and valuable addition to the literature and is just the type of work which the student and practitioner require.

J. T. INGRAM.

CHEMICAL INDUCTION OF CANCER

Chemical Induction of Cancer. By George Wolfe, B.Sc., D.Phil. Foreword by Professor Alexander Haddow. (Pp. 250. 17s. 6d.) London: Cassell and Co. 1952.

This work is a general compilation of all that is known on the induction of cancer by substances of known constitution. Professor Alexander Haddow in his introduction says: "So far as concerns the experimental reproduction of the disease and the understanding of the biological process involved, no more useful or more succinct general account can be recommended than that in the pages which follow," and the reviewer could not improve on this statement.

The book can be recommended for the general medical and biological reader who wishes to have exact information on this subject. Very wisely, the author begins with a readable general account of the structure of condensed carbon ring compounds; it will certainly be useful to the general reader. He then, through subsequent chapters, reviews the various types of compounds with carcinogenic activity, and discusses in other chapters their possible mode of action, effects on enzyme systems, and their metabolism in the body. The work is well indexed and will be valuable in any medical or biological library.

E. C. DODDS.

MOLLUSCICIDES

Molluscicides. By Alan Mozley, D.Sc., Ph.D., F.R.S.Ed. (Pp. 88; illustrated. 9s.) London: H. K. Lewis and Co. 1952.

This manual should be of interest to readers who wish to learn the main facts about molluscicides and how they are applied. The author outlines their importance in controlling diseases of man and animals caused by trematode parasites and discusses their toxicity (to organisms other than snails), the preliminaries to application, and the different methods of applying them. Three kinds of molluscicides are recognized—those of vegetable origin, synthetic organic substances, and inorganic salts. The fruits of some species of *Balanites, Swartzia,* and *Sapindus* contain saponins which are toxic to snails. The roots and rhizomes of *Derris* spp. and the leaves and flowers of *Tephrosia* spp. also contain molluscicidal substances. The author thinks that neither these nor the synthetic organic substances—the latter are the subject of much research at present in America—include the ideal molluscicide. He favours the salts of copper, especially the sulphate and the carbonate, but considers that members of the other two groups may be used advantageously in conjunction with copper salts.

In four appendices the author describes briefly the life cycles of *Schistosoma* and *Fasciola;* gives directions for finding snails and examining them for infection; reports a field experiment conducted by himself in Southern Rhodesia; and gives practical instructions for treating a pond, pool, tank, or swimming bath with copper sulphate.

J. J. C. BUCKLEY.

RHEUMATIC DISEASES

Rheumatic Diseases: Diagnosis and Treatment. By Eugene F. Traut, M.D., F.A.C.P. (Pp. 942; 192 illustrations. £7 10s.) London: Henry Kimpton. 1952.

This is an ambitious and well-produced volume intended to review the whole field of the rheumatic diseases. It is produced by a group of physicians working in and around Chicago, but appears in places to reflect their personal preferences and prejudices rather than, as is their avowed intention, current world opinion. There are indeed very few references to work published outside the United States. Examples of these personal views will be found in the advocacy of vaccine treatment, the statement that gold salts cannot be recommended as a safe therapy, and the importance still placed on focal infection. The arrangement and nomenclature of the chapters will also prove rather puzzling to English readers; for example, although Chapter 3 is entitled "Psychologic Factors in Rheumatoid Arthritis," there is no separate chapter on adult rheumatoid arthritis, nor on osteoarthritis, although these entities are naturally well covered, incidentally, in the text.

This is one of those books that one feels would have been a great deal better if the editor had been content with half its present size. It is nevertheless a valuable acquisition for the rheumatologist's library, since it provides an interesting and somewhat unusual viewpoint of the subject and is extremely well illustrated.

W. S. C. COPEMAN.

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FIRST WORLD CONFERENCE ON MEDICAL EDUCATION

As has already been announced in this *Journal*[1] the First World Conference on Medical Education will be held in London in August of this year, under the presidency of Sir Lionel Whitby, Vice-chancellor of Cambridge University; the deputy president is Professor W. Melville Arnott, of Birmingham University. The Chancellor of the University of London, the Secretary of State for Scotland, and the Ministers of Education and Health for England and Wales have kindly agreed to act as patrons. Elsewhere in this issue (p. 503) we give details of the programme.

The work of the Conference will be carried on in the four principal sections meeting simultaneously throughout the week, under the chairmanship of the four vice-presidents of the Conference: Dr. Victor Johnson, Director of the Mayo Foundation, Sir A. T. Mudaliar, of the University of Madras, Professor Alberto Hurtado, of the University of San Marcos, Lima, and Professor René Sand, of the University of Brussels. They will be in charge respectively of the following sections: "Requirements for Entry into Medical School," "Aims and Content of the Medical Curriculum," "Techniques and Methods of Medical Education," and "The Teaching of Preventive and Social Medicine." Doctors from many countries have already accepted invitations to speak at the Conference, which promises, therefore, to provide a real opportunity for an international exchange of views on the important topic of medical education.

The World Medical Association initiated the Conference, and it is being held under its auspices, the British Medical Association, as a member of the W.M.A., acting as the host organization and making itself responsible for the local arrangements. The World Health Organization has joined with the W.M.A. in sponsoring the Conference and has a special interest in the fourth section of the programme —"The Teaching of Preventive and Social Medicine." The C.I.O.M.S. (Council of International Organizations of Medical Sciences) has also been of great help to the Organizing and Programme Committees, as, too, has the I.A.U. (International Association of Universities).

In the conception and planning of the Conference, therefore, three international organizations under the W.M.A. have taken an active part and will continue to do so; it is hoped the outcome will be of value to those responsible for medical education in different parts of the world. Limitations of time and money will unfortunately make it difficult for medical educators from far distant countries to be present in London in August, but there will be as wide a representation as is possible in the circumstances. The three official languages of the meetings will be English, French, and Spanish, and simultaneous translation will be available in every session. The Conference will be open to members of the medical profession and also to non-medical teachers who may have a special interest in some of the subjects of the programme.

The general theme of the Conference is undergraduate medical education, and no attempt will be made to go beyond this into discussions on postgraduate education—which one of these days may well be the subject of another congress. As the titles of the themes given in the programme may suggest, the aim will be to concentrate on principles and methods rather than on the minutiae of the medical curriculum. It would, in fact, be impossible to try to draw up in August this year the details of a curriculum which would satisfy even the different medical schools of Britain. The title of Sir Lionel Whitby's Presidential Address, "The Challenge to Medical Education in the Second Half of the Twentieth Century," provides the keynote of the meeting. In the programme there are, of course, certain well-worn themes of medical education, and it is hoped that the principal speakers at the Conference will not hesitate to challenge some of the conceptions that traditionally lie behind these. There will, too, be discussion on themes that are new, or at least new in relation to present medical curricula in the various countries. In the section "Requirements for Entry into Medical Schools," schoolmasters and medical men will exchange views on the subject "General Education in an Age of Science." The type of human being the future doctor will be will depend to a large extent on the kind of education he has

[1] *British Medical Journal*, 1952, **2**, 480.

at the secondary school stage. Reports on medical education so often pay lip service to the need for a broad education in the humanities, and then we see our ancient universities in this country insisting that a boy or a girl should pass the First M.B. before going, for example, to Oxford or Cambridge. This often forces the schoolboy into specialization in the basic sciences, and the schoolmaster, with the examination hurdle in mind, finds it difficult to provide an education that will fit the boy to be an intelligent citizen of the world. The programme, too, suggests a different approach to the First M.B. itself in providing for a discussion on "The Teaching of the History of Science" and of "The Scientific Method," and on "The Introduction to the Social Sciences." The Conference may decide that room could, or even should, be found for such subjects at the First M.B. stage, and this could be done if the student was less burdened with memorizing a large number of facts and formulae in order to protect himself against the unkind tricks the examiner may play on him. In the second section of the Conference surgeons and physicians will take a prominent part in the discussions on the teaching of anatomy and physiology, and the movement towards a new conception of this is shown in the title "The Integration of Physiology and Anatomy as a Single Subject in the Medical Curriculum." The title "Science is Measurement" in the premedical phase of the curriculum suggests that the Programme Committee would like to see some continuation of the teaching of mathematics so as to prepare the student for an introduction in the Second M.B. period to medical statistics.

Recent reports on undergraduate medical education stress that its aim is to produce an educated doctor and not any one particular type of doctor. Indeed, if we are to maintain and substantiate our claim to be a learned profession the teaching of medicine must be imbued with the university ideal. If the foundations are well and truly laid on the basis of principle and method, then the other things will be added with no great difficulty, whether the qualified doctor is to go into general practice, specialist practice, research work, teaching, or administration. Nevertheless, the majority of medical students will, after qualification, go into the most strenuous branch of medicine—that of general practice. The Programme Committee has therefore arranged for discussions on "The Undergraduate and General Practice," "Teaching in the Home," and "The Home Setting in Medical Education," these three subjects being dealt with in different sections. It is hoped general practitioners will take an active part in the open discussion on these, as well as on other subjects. One morning will be given to a review of visual aids in medical education, and to supplement this the Film Committee of the B.M.A. expects to arrange a demonstration of visual aids in the intervals between the morning and afternoon sessions during the week.

August has its disadvantages as a month in which to hold a conference, but it is a month in which medical teachers can take a busman's holiday without leaving their students in the lurch. Many distinguished medical men are coming from various parts of the world to say their piece and to listen and perhaps learn from others. Apart from the work of the sections, they will welcome the opportunity of meeting their colleagues from other countries, and in particular from Britain. Time and money inevitably limit the number of persons who can be specially invited to speak, but time has been allowed for open discussion of each subject in each section. It is hoped that as many as possible of the teaching staffs in Britain will find it possible to attend at least part of the Conference so that they can meet and welcome their colleagues from abroad. The W.M.A. itself is anxious that the "practising physician," as, so to say, the consumer of medical education, will also seek to make his voice heard in the debates in the four main sections of the Conference.

RESPIRATORY FUNCTION

It has been said that science is measurement. But this is only partially true, for there is much that is merely qualitative description and reasoning in the content of science. Nevertheless, when a body of knowledge passes from the qualitative to the quantitative stage notable advances occur. Quantitative study of respiratory function is a case in point. The problem in this field is not only what to measure but also the assessment of the significance and relationship of the many measurements which can be made. In hardly any other branch of human physiology is it possible to amass so many figures in so short a time. Many investigators have tended to confine their observations more or less exclusively to one particular variable of respiratory activity. There have been those who have measured static volumes of the lungs, others have concentrated on rates of mixing, while the more sophisticated have realized the paramount importance of ventilation–perfusion relationships. Other workers have appreciated the indissoluble partnership between the circulatory and respiratory

systems and have brought to the study of pulmonary function the cardiac catheter and all its possibilities of pressure-flow measurements in the heart and lungs.

All this new knowledge is not exclusively a matter of academic science but of vital importance to patients. The obliteration of the tuberculous cavity and the removal of the neoplasm necessitate profound structural alterations of the respiratory system. Such questions as, "What is his respiratory function at present?" and, "How can we control this disease with a minimum loss of respiratory function?" arise continuously in thoracic medicine. It is only by the careful study of pulmonary function before and after various operations and other therapeutic procedures that the answers to the latter question will be obtained. An accurate answer is as important as a good histopathological report on the biopsy specimen. Dr. K. W. Donald in the two articles we have published in this and last week's *Journal* has given a most helpful, and much-needed, survey of respiratory function and reviewed the relative value of many different methods of investigation. All aspects of respiratory function are subservient to the efficient exchange of oxygen and carbon dioxide between blood and atmosphere. Spirometric studies alone have obvious limitations, and Donald recommends beginning with ventilatory studies, proceeding as experience is gained to arterial blood studies, and ultimately to consideration of ventilation–perfusion relationships. He also emphasizes that the effect of lung disease on the right heart is a relatively unexplored subject which would repay investigation with clinical rewards.

Donald's paper makes it plain that respiratory physiology is a matter which closely concerns the clinician. A sound knowledge of cardio-respiratory physiology adds greatly to clinical acumen and the correct interpretation of physical signs. As a result of recent physiological studies the physician is now able to recognize interference with oxygen diffusion in the lungs with tolerable certainty. The dangers of carbon-dioxide narcosis in oxygen tents have also been pointed out to the previously unsuspecting clinicians. The grave import of even slight cyanosis with a normal cardiac output and blood count is another urgent clinical matter: such patients may have an arterial blood saturation below 50% at a time when there is still doubt whether significant cyanosis is present. Many of these measurements require the presence of the patient in the laboratory, and it is now time to regard such investigations with something more than the usual good-tempered indulgence towards a few pioneering back-room boys. Clinicians investigating thoracic disease might well consider devoting as much personal attention to the assessment of respiratory function as they do to the discussions with the pathologist, to radiological screening, and to surgical operation. Physiological studies cannot be established and made useful in a short time. Practice and experience in their application, in constant association with clinical medicine, are required before rich dividends are likely. British workers in this field have no grounds for complacency. The main recent developments in both theory and practice have occurred in the United States. It is an illuminating experience to go from centre to centre there and see how extensive physiological studies are made on patients with respiratory disease and how such studies condition and improve the clinical work. For many years now radiology and morbid anatomy have been the predominant tools of clinical investigators in this country. Essential as these are, clinical physiology should now play its full and equal part in the practice of thoracic medicine and surgery.

A JOURNAL AND ITS READERS

Under this title the Editor of the *New England Journal of Medicine* recently observed[1] that "the most prominent feature of any journal is its original papers," and that, "obviously, few papers will be of universal interest to all the Journal's readers." He quotes with approval the comment of the Editor of *Science* that a journal is not so much what "its editors would like it to be, as what its contributors make it." And so it is with the *B.M.J.* In attempting to carry out the first object of the B.M.A.—"to promote the medical and allied sciences"—the *Journal* follows the sound tradition of putting first things first, and in an art and science practised by a learned profession the first things are contributions to knowledge, contributions, in the nature of things, varying in importance and interest to the generality.

Clifford Allbutt said in 1919 that medicine was becoming less of an art and more of an applied science. What would he have said to-day? Those of our readers who are at the peak or over of middle age must find the pace of medical research fast and furious, and the expression of it in the printed pages of medical literature tough going. What appears in the *B.M.J.*, and in other similar journals, is but a reflection of work in progress; it represents the results of investigations made by medical men into

[1] *New Engl. J. Med.*, 1952, **247**, 577.

the causes and effects of disease and into the conditions of health. In these investigations there can scarcely be a science whose aid is not brought in to help to solve the problems of medicine; and so the language of medicine becomes scientifically ever more polyglot, and the tools it uses have to be applied with ever greater precision. It is more difficult than before for the "average" doctor (if there is such a person) to keep up to date, or even, on occasion, to understand the scientific ins and outs of a medical paper: indeed, it is probably easier for his medical student son or daughter. But that is the penalty of progress in medical science. As the Editor of the *New England Journal of Medicine* stresses, "a function of a journal such as this is to present the results of original investigations and observations in *any* field that pertains to medicine." The *B.M.J.* is a "journal such as this," and with its circulation in the region of 78,000 copies weekly goes to all kinds of doctors in all parts of the world. It is not a journal for general practitioners, or consultants, or public health officers, or laboratory workers. It is a journal which aims at representing the best of British medicine in order to "promote the medical and allied sciences." It tries to provide each week something for everybody, not everything for somebody.

The general practitioner, it is true, is specially catered for in the "Refresher Course" series and in "Any Questions?" But it may be questioned whether the multiplication of journals for general practitioners is a healthy tendency in medical journalism. It is a tendency which has behind it the assumption that the general practitioner is intellectually inferior to his colleagues, that for him medicine is somehow a different kind of profession than it is for others, that medical science in the making is something from which he should avert his eyes as being beyond his understanding. This tendency, carried to its limit, would make medical science and research esoteric mysteries into which the G.P. would not be initiated. We can think of nothing that would in the long run be more detrimental to the prestige and welfare of the G.P., or more harmful to medicine.

A journal such as the *B.M.J.* tries to put before its readers the whole of medicine, not just parts of it. It can do this because all medical men have had the same basic training and intellectual discipline; all are members of a learned profession. No reader should, we suggest, expect to find something of special interest to him on every page or, indeed, in every section of the *Journal*; any more than he should expect to find something of special interest to him in every section, say, of *The Times*. To those who find the substance of some original articles hard to digest we can but offer apologies on behalf of modern medicine, the hard taskmaster of us all and in the last resort provider of the matter which fills these pages.

THROMBO-ANGIITIS OBLITERANS

Buerger regarded thrombo-angiitis obliterans as a specific inflammatory disease of unknown cause leading to progressive obliteration from the periphery of the vessels of the leg, occurring before the age of 40, affecting mainly Jews, and sometimes causing also a migrating thrombo-phlebitis. Subsequent recognition of other causes of vascular occlusion in the same age group has led to difficulties in diagnosis which are outlined by Dr. R. L. Richards elsewhere in this issue. As he points out, it is now agreed that Buerger's disease has no special predilection for the Jewish race. Nor is venous thrombosis a pathognomonic sign, for Lisa, Magiday, and Hart[1] found it in 19 of 53 limbs amputated for arteriosclerosis. Even the specificity of the pathological findings has been questioned by Boyd and his colleagues,[2] though most authorities do regard the histological changes as distinct from those seen in other forms of occlusive vascular disease.

Remarkably few cases with histological proof have been recorded, and analysis of the clinical features of large series of cases, whose true pathological basis is often in doubt, has done little to clear up the difficulties in diagnosis. Of Richards's 85 cases, 22 had the diagnosis proved pathologically, but unfortunately he has not analysed these separately. The diagnosis has been disproved in two of the other cases, and Luke's experience[3] suggests that many more may not in fact be examples of Buerger's disease. Luke made histological examinations of leg arteries from 19 patients in whom a diagnosis of thrombo-angiitis obliterans had been made on clinical criteria similar to those adopted by Richards, and was able to confirm the diagnosis in only four cases.

Richards states that one of the two criteria which remain reliable indications for a diagnosis of thrombo-angiitis obliterans is the constant association with tobacco smoking. Telford,[4] however, refers to undoubted cases in men who had never smoked. The traditional view that heavy smoking predisposes to the development of the disease is based almost entirely on clinical impressions. Harkavy, Hebald, and Silbert[5] found positive skin tests to extracts of tobacco smoke in 83% of 68 patients with Buerger's disease and in only 10% of 107 controls. Sulzberger[6] found positive skin

1 *J. Amer. med. Ass.*, 1942, **118**, 1353.
2 *J. Bone Jt Surg.*, 1949, **31B**, 325.
3 *Canad. med. Ass. J.*, 1947, **56**, 377.
4 *Lancet*, 1937, **1**, 549.
5 *Proc. Soc. exp. Biol. (N.Y.)*, 1932–3, **30**, 104.
6 *J. Amer. med. Ass.*, 1934, **102**, 11.
7 *British Medical Journal*, 1951, **2**, 1007.

tests to tobacco extract in 78% of 24 patients with Buerger's disease; of his controls, 36% of 95 smokers and 16% of 58 non-smokers gave positive tests. However, almost as high a percentage of the patients with Buerger's disease gave positive tests to other allergens, and the results of the skin tests cannot be regarded as strong evidence of a special association between the disease and smoking. Shepherd[7] appears to have established that cigarette smoking leads to constriction of peripheral vessels, so that patients with all forms of arterial insufficiency should certainly try the effect of giving up smoking. But a properly devised statistical investigation is needed before a history of heavy smoking from a patient with occlusive vascular disease can be regarded confidently as a point in favour of the diagnosis of thrombo-angiitis obliterans.

INTRINSIC FACTOR

Ever since the pioneer experiments of Castle[1] research workers have striven to purify and identify the "intrinsic" and "extrinsic" factors. Within recent years extrinsic factor has been identified as vitamin B_{12},[2] but the exact nature of intrinsic factor is still undetermined. Nevertheless much is known about the properties of intrinsic factor, and recent work in the U.S.A. has led Glass and his co-workers[3 4] to suggest that one of the components of gastric mucin, "glandular mucoprotein,"[5] might be identical with it, or at least be the main carrier of intrinsic factor in human gastric juice. Certainly the similarities in behaviour from the laboratory point of view between glandular mucoprotein and intrinsic-factor-containing material are close. Moreover, glandular mucoprotein has been shown to be absent from, or present only in traces in, gastric juice from patients with pernicious anaemia.[4] The American workers found that daily oral doses of 50–75 mg. of glandular mucoprotein given with 30 μg. of vitamin B_{12} usually sufficed to produce optimal haematological responses in patients with pernicious anaemia.

In the opening pages of this issue Drs. A. L. Latner and C. C. Ungley, with their associates, describe work which has been proceeding in Britain on rather similar lines. Normal gastric juice was ultrafiltrated, freeze-dried, and finally reconstituted in a concentration 150–200 times stronger than the original. The concentrates were submitted to filter-paper-strip electrophoresis. Liquid from segments of the filter-paper strips was then tested for B_{12}-binding activity by microbiological assay and also for haemopoietic activity when given to patients with pernicious anaemia as a single oral dose, together with 50 μg. of vitamin B_{12}. Two peaks of B_{12}-binding and haemopoietic activity were demonstrated as a result of electrophoresis of the gastric-juice concentrates; one was on the cathode side and the other on the anode side of the starting point. The material from the anode peak was more active haemopoietically, and Latner and Ungley state that this material contained either a mucoprotein or a mucopolysaccharide. They claim also that the material at the cathode peak, although containing more mucoprotein, had less intrinsic-factor activity.

Thus important progress in the identification of intrinsic factor has been made both in the United States and in this country. Neither group of workers claim, however, that they have isolated intrinsic factor in a pure form. Have these advances a practical bearing on the treatment of pernicious anaemia? Enough human gastric juice will never be available for human intrinsic factor to be prepared on a commercial basis, but if intrinsic factor could be extracted economically from animal stomachs in a sufficient degree of purity, then the taking of perhaps a few milligrams of the material with a still smaller amount of vitamin B_{12} in the form of a small capsule would be a way of treating pernicious anaemia which would be most convenient from the patient's point of view. On the other hand, crystalline vitamin B_{12} is now readily available at a low price, and if given intramuscularly in sufficient dosage at two- or four-weekly intervals it provides a highly effective method of treatment. It has, too, the advantage over oral therapy that the patient necessarily remains under the doctor's personal supervision.

1 *Amer. J. med. Sci.*, 1929, **178**, 748.
2 Gardner, F. H., Harris, J. W., Schilling, R. F., and Castle, W. B., *J. Lab. clin. Med.*, 1949, **34**, 1502.
3 *Fed Proc.*, 1951, **10**, 50.
4 *Science*, 1952, **115**, 101.
5 Glass, G. B. J., Boyd, L. J., and Svigals, C. S., *Bull. N.Y. med. Coll.*, 1950, **13**, 15.

CHLOROFORM IN OBSTETRICS

In November, 1847, Professor James Young Simpson first used chloroform to relieve the pains of childbirth. Three months later the first death due to it was reported. Later the scientific papers, conferences, and commissions of the mid-Victorians clearly showed their concern at the death rate associated with so promising a drug. In the twentieth century we are still trying to find safer substitutes. But at least the causes of death have been clarified: they fall into three groups.

The first comprises cases of sudden cardiac arrest during light anaesthesia. The condition may be due to either ventricular fibrillation or ventricular arrest. Despite ideal conditions, there were four cases of ventricular arrest in Waters's series[1] of 1,000. His patients would have died had not all the facilities for resuscitation been available. Many will think these figures are enough to condemn the use of chloroform outside highly organized operating-theatres, and especially in the patient's own home. The second group of fatal cases comprises those of gradual cardiac and peripheral circulatory failure in the deeper planes of anaesthesia. This complication is easily recognized nowadays and can be treated promptly with oxygen and lowering of the head. The third group is of cases where liver failure occurs two to three days after the administration. Elsewhere in this issue Mr. R. L. Lunt describes three cases of jaundice in the puerperium following the use of chloroform for the delivery. Waters concluded that

1 *Chloroform, A Study after 100 Years.* Wisconsin, U.S.A.: University of Wisconsin Press. 1950.
2 See leading article in *British Medical Journal*, 1953, **1**, 443.

chloroform caused only slightly more liver dysfunction than other anaesthetic agents. It is probable that the combination of the factors described by Mr. Lunt with the metabolic derangement resulting from any anaesthetic is more important in the causation of liver failure than any specific anaesthetic drug.

No single agent has been found with all the advantages of chloroform, although there are many which, when combined, give better results with greater safety. Chloroform has therefore lost its place in the anaesthetic room and operating-theatre to linger in its original domain—the home of the woman in labour. Here a single drug which is portable, non-inflammable, potent, and reliable is ideal, but if the risk of using chloroform in domiciliary obstetrics is not justified then safe and convenient substitutes must be provided. For intermittent analgesia the combination of pethidine and nitrous oxide and air supervised by the midwife is fairly satisfactory. The adoption of a safe automatic trichlorethylene inhaler for use by the midwife would improve the service she could give her patient.[2] For forceps delivery and other manœuvres, when there are no fires or naked flames, ethyl chloride followed by ether on an open mask is a good and safe anaesthetic. Fires can sometimes be extinguished, but when this is not possible, or when lighting is dependent on gas or oil, or in great urgency, intravenous thiopentone in small dosage can be given and anaesthesia maintained with trichlorethylene and air. This technique should be used only if the administrator is confident that he can maintain a good airway and treat apnoea by controlling the respiration with a simple inflator.

GREASE ON THE SKIN

The skin is a self-sterilizing surface. *Streptococcus pyogenes* does not survive very long on it, and some other pathogenic bacteria are apt to die out. Ringworm has been known to clear spontaneously at puberty when the secretion of fungicidal fatty acids increases, while adult hair is protected against infection by its covering of such fatty compounds. It is the semi-fluid surface grease or sebum from the sebaceous glands which gives this protection, and the body produces 1–2 g. daily, half of it on the scalp.[1] This is enough to give a layer 0.7 μ thick, which would be visible in histological sections of skin if the usual preparative methods did not dissolve it off. The layer is not evenly spread over the whole body surface, being most noticeable on nose and forehead and over the shoulders, while in the ear and on the glans penis it is modified as cerumen and smegma respectively. Although attempts to study it have been going on for over 40 years, recent biochemical techniques, in particular new methods for microanalysis, are now making possible the study of the sebum from a single individual, or even from a single patch of his skin. It is hoped that differences or changes will be noted not only in various skin diseases but in general metabolic disorders, throwing fresh light on the obscurities of fat metabolism. In the meanwhile results are already affecting the treatment of skin infections.

Sebum from the skin of the forearms has been chiefly investigated so far. It is dissolved off by plunging the arm into a jar of acetone and holding it there for three minutes. Each arm yields about 50 mg. of sebum; the skin so exposed secretes a new layer of normal thickness in about two hours.[2] Analysis of the dissolved material[3] shows it to be a fatty mixture: 50% is neutral fat (triglyceride or other ester), 5% cholesterol, 30% free fatty acid, and the rest hydrocarbon, including 5% squalene ($C_{30}H_{50}$), a substance previously found in shark liver oil and yeast and also in the lipid of ovarian dermoid cysts. What function this and the other hydrocarbons serve on the skin surface is a physiological mystery. Squalene with its six double bonds has a slight resemblance to carotene and part of vitamin A. Applied pure to the skin of rabbits and guinea-pigs, it causes a reversible baldness, but whether it plays any part in human alopecia is unknown.[4] It is noteworthy that sebum contains no vitamin A or D, in spite of their associations with skin physiology, and vitamin E is probably also absent.[5]

About one-third of normal sebum is free fatty acid, and that is the fraction responsible for repelling bacterial or fungal attack. There are two types of acid involved. One-third of the total consists in saturated fatty acids like the stearic acid of ordinary body fat but about half the molecular size. Whereas stearic acid has seventeen carbon atoms in a chain, the sebum saturated acids have only seven, nine, eleven, or thirteen. They are antagonistic to *Microsporon audouini*, a ringworm fungus, and are now sold for therapeutic use. The other two-thirds of the fatty acids are unsaturated, and are bactericidal, particularly oleic acid. Squire and his co-workers[3] have shown that the self-sterilizing power of the skin depends on these acids and on the maintenance of dryness. Streptococci and micrococci disappear from the skin in a few minutes under these conditions; *Staph. aureus* goes slowly, while *Bact. coli* and *Ps. pyocyanea* are resistant and remain unharmed. Corynebacteria, mycobacteria, and *H. pertussis* are also fatty-acid sensitive. On the other hand Dr. F. A. Whitlock concludes in an article on another page that *Pityrosporum ovale* is a harmless organism on the scalp and thrives in a heavy flow of sebum. Burtenshaw,[6] in a review of the earlier work on this subject, pointed out that individuals differ in the bactericidal power of their skins. Another factor influencing individual variations in skin pathology is the presence of moisture, which impairs the bactericidal efficiency of the fatty acids; and stagnant damp in interdigital clefts and skin folds helps to explain their vulnerability to infection.

Two practical conclusions result. One is that skin dressings should be non-absorbent but permeable for evaporation. Nylon, which is unwettable, is much to be preferred[2] to the ordinary cotton gauze, which becomes damp and wets the skin under it. The other is that cleaning of the skin for vaccination and the like is best done with soap and water, which never removes more than a quarter of the protective sebum,[3] while ether and acetone on the contrary wash it all off and leave the skin bare for over an hour afterwards.

[1] Cameron, G. R., and Short, R. H. D., in MacKenna, R. M. B., *Modern Trends in Dermatology*, p. 54. London: Butterworth. 1948.
[2] Ricketts, C. R., *et al.*, *Clin. Sci.*, 1951, **10**, 89.
[3] MacKenna, R. M. B., *et al.*, *J. Invest. Derm.*, 1950, **15**, 33.
[4] Flesch, P., and Hunt, M., *Arch. Derm. Syph. (Chicago)*, 1952, **65**, 261.
[5] Festenstein, G. N., and Morton, R. A., *Biochem. J.*, 1952, **52**, 168.
[6] In MacKenna, R. M. B., *Modern Trends in Dermatology*, p. 158. London: Butterworth. 1948.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

TACHYCARDIA

BY

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Palpitation is a very common symptom, and, since it is often due to tachycardia, the various causes of this disorder merit careful consideration. It is convenient to classify cases of tachycardia in two main groups—those in which the tachycardia is due to simple acceleration of the normal sinus rhythm and those in which it results from the incidence of some abnormal rhythm.

I. ACCELERATION OF THE NORMAL SINUS RHYTHM

Before enumerating various conditions responsible for this type of tachycardia brief reference must be made to certain physiological principles bearing on the subject.

The cardiac reserve is a measure of the extent to which the heart is capable of raising its output to meet the oxygen requirements of the body during physical exertion, and, since the output per minute is the product of the output per beat and the heart rate, the smaller the increase in stroke volume the greater must be the increase in heart rate to achieve an equivalent increase in output. Comparative physiology provides an interesting illustration of the relation of heart rate to stroke volume. Animals capable of prolonged and severe exertion have slower pulses than sedentary animals. For example, the resting pulse rate of the hare, an exceedingly athletic animal, is under 70, while that of its cousin, the rabbit, a sedentary creature, which seldom strays far from its burrow, is over 200. To compensate for this difference in pulse rate, the hare's heart, relative to its body weight, is three times as big as the rabbit's. It seems to be a general law throughout all warm-blooded animals, both birds and mammals, that those with big hearts have slow pulses and vice versa.

The increase in pulse rate produced by exercise and the time taken to return to the resting rate following exercise have been widely employed in attempting to assess cardiac efficiency. The test employed by National Service medical boards in the examination of recruits was to place one foot on a stool about 18 in. (45 cm.) in height and to raise the body 20 times in 60 seconds. In healthy subjects in good physical training the pulse should return to the resting rate within one minute of the cessation of exercise.

We may now consider certain conditions in which physical exertion causes excessive tachycardia.

In many types of heart disease the stroke volume of the heart is reduced and, consequently, to increase output the heart has to beat faster than in health. But, short of actual disease, tachycardia on exertion may be due simply to physical unfitness resulting from obesity, excessive smoking, lack of exercise, and other causes; in patients with organic heart disease physical unfitness will add to their disability.

The term "effort syndrome" was coined by Lewis in the first world war to describe a condition in which the response of the circulatory and respiratory mechanisms to exertion was excessive in subjects without disease of either heart or lungs. In these patients the ability to perform muscular work is decreased and mild exertion causes breathlessness, palpitation, and other symptoms; the increase in the heart rate after exercise is greater than in health, and it takes longer for the pulse to return to its resting rate. It is now recognized that purely psychogenic factors are responsible for many of these cases, but a similar clinical picture is seen in patients convalescent from an acute illness such as influenza.

In addition to exertion, emotion may induce tachycardia, in fact clinically it would probably be true to say that nervousness is the most common cause of tachycardia. Many perfectly healthy people are scared at the mere thought of a medical examination, especially when their fate may be determined thereby, while others become unpleasantly heart-conscious when called upon to get up and make a speech. One of my patients, a keen bridge player, told me that this lack of control proved most disconcerting, for whenever she picked up a particularly good hand her heart always started to race and consequently her murmur became audible to her opponents and gave the show away.

During the war National Service medical boards referred many recruits for a second opinion on account of persistent tachycardia. Was the tachycardia physiological or was it pathological? In point of fact it was generally due to fear of being rejected. When, in addition to tachycardia, the recruit had a systolic murmur, as was often the case, for overaction of the heart may produce such a murmur, an especially careful search for other signs of heart disease was indicated. In these recruits the possibility of thyrotoxicosis had to be considered, but even in the absence of thyroid enlargement or exophthalmos the diagnosis rarely presented much difficulty.

Acceleration of the normal sinus rhythm may be due to many other causes, but those mentioned above—namely, heart disease, physical unfitness, the effort syndrome, thyrotoxicosis, and nervousness—are clinically the most important when the patient's principal complaint is palpitation.

II. TACHYCARDIA CAUSED BY AN ABNORMAL RHYTHM

This type of tachycardia may occur either in paroxysms or as an established disorder. In paroxysmal tachycardia the heart rhythm is regular and the rate generally between 140 and 240 per minute. The paroxysm is, in fact, nothing more or less than a long series of premature beats with no intervening normal cycles, and, as in the case of premature beats, the ectopic focus from which the paroxysm arises may be either supraventricular or ventricular.

Supraventricular Paroxysmal Tachycardia

This type of paroxysm often occurs in people in whom there is no evidence of organic heart disease. Provided the paroxysm is not prolonged, it is not dangerous, but it may be very distressing and even alarming to the patient. Unlike tachycardia due to simple acceleration of the normal sinus rhythm, which arises in response to some obvious physical or nervous stimulus and abates when that stimulus is removed, these sudden bouts of tachycardia start abruptly at any time and for no apparent reason; not infrequently the attacks seem to be associated with a digestive disturbance, but whether this is a causal factor or not it is difficult to say.

Since we rarely have the opportunity of actually observing an attack, the diagnosis has generally to be based on the patient's description of his symptoms. The most characteristic feature is the abrupt transition from the normal to the rapid rate of beating, but not infrequently the paroxysm

is preceded by a short bout of irregular heart action due to extrasystoles (Fig. 1). Patients sometimes say that the attack terminates equally suddenly with a "thump." This is due to the forcible beat following the long compensatory pause which precedes the re-establishment of normal rhythm. In other cases the heart slows down gradually and imperceptibly. Unlike nervous tachycardia, the rate is unaffected by change of posture. The duration of paroxysms varies from a few minutes to a few days, or occasionally longer, but in most cases it lasts from two to twelve hours. When the attack is of long duration acute cardiac dilatation and congestive heart failure may supervene.

The disability experienced during an attack varies greatly in different individuals. In addition to palpitation, some

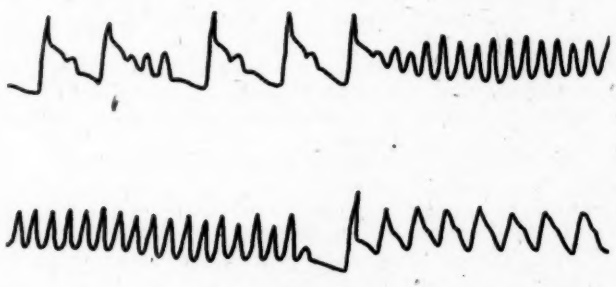


FIG. 1.—Sphygmogram showing short paroxysm of tachycardia, preceded by a period of irregular heart action, due to extrasystoles, and followed by normal rhythm. Note forcible beat following end of paroxysm.

patients complain of anginal pain due to coronary ischaemia, others suffer from manifestations of cerebral anaemia, such as dizziness or even actual syncope. I have, however, occasionally met with patients in whom the disorder of rhythm produced so little subjective disturbance that they were able, admittedly with difficulty, to carry on their normal occupations.

Attacks may terminate in vomiting, and can sometimes be aborted by inducing vomiting by tickling the back of the throat; pressure on the carotid sinus or on the eyeball will sometimes stop an attack; but, although these various tricks are worth trying, none of them is infallible. Fortunately most attacks stop spontaneously. In prolonged attacks, quinidine sulphate by mouth is the most useful remedy: 6 gr. (0.4 g.) should be given two-hourly for five doses, and a similar amount on two successive days if the attack persists. Intravenous quinidine should be used only in cases of exceptional urgency. Full digitalization (1 mg. of digoxin intravenously, followed by 0.5 mg. six-hourly) is sometimes successful in cases which fail to respond to quinidine. Of the cholinergic drugs, which have been used in prolonged attacks, methacholine ("amechol," "mecholyl"), 10–20 mg. subcutaneously, is the most reliable, but is apt to cause unpleasant side-effects. Recently procaine amide has been employed as an alternative to quinidine, but a difference of opinion still exists regarding the relative merits of these two drugs. Oral administration is apt to produce nausea and vomiting, and ventricular fibrillation has been reported when procaine amide was given intravenously. Some workers have reported favourably on intramuscular injection. It is said to be more effective in the ventricular than in the supraventricular type of paroxysm.

Ventricular Paroxysmal Tachycardia

Ventricular can be distinguished with certainty from supraventricular paroxysmal tachycardia only by the electrocardiogram, but its presence may be suspected clinically from the fact that, whereas the latter commonly occurs in an otherwise healthy subject, the former is generally associated with serious heart disease. It may occur as a complication of acute coronary occlusion or may be initiated by mechanical stimulation in the course of surgical operations on the heart or cardiac catheterization, so that when performing such manipulations it is customary to give the patient quinidine or procaine amide as a prophylactic measure. In view of its seriousness, this complication should be regarded as a medical emergency requiring immediate admission to hospital, and its treatment hardly comes within the scope of the present article.

Auricular Fibrillation

This arrhythmia may be either permanent or paroxysmal. Paroxysmal auricular fibrillation is a not infrequent precursor of the established condition in patients with rheumatic or degenerative heart disease. Less commonly the paroxysms recur at more or less regular intervals over periods of years in apparently healthy subjects. The gross irregularity of the heart's action during the attack is generally obvious to the patient and will suffice to distinguish the condition from paroxysmal tachycardia.

In paroxysmal fibrillation the change from normal rhythm to fibrillation may prove most distressing to the patient, and one of my medical colleagues who suffered from such attacks, though otherwise his heart seemed to be perfectly normal, tells me that the sense of increased well-being when, after many years, he became a permanent fibrillator was quite remarkable. When attacks recur frequently continuous digitalization is indicated, in order to control the ventricular rate during the paroxysms. Quinidine, 3 gr. (0.2 g.) twice a day, may reduce the frequency of attacks, but often it has little beneficial effect.

Established auricular fibrillation is generally associated either with advanced rheumatic or degenerative heart disease or with thyrotoxicosis, but it has in rare instances been reported to follow an electric shock or other forms of trauma.

Uncontrolled fibrillation is easily recognized by the fact that it is the only type of tachycardia associated with grossly irregular heart action. From time to time two or more beats follow each other in very rapid succession. When this happens the ventricle contracts before it has had time to fill with blood. Such beats are ineffective on account of the small output of the heart, and only a very feeble pulse wave (Fig. 2), or it may be no pulse wave at all,

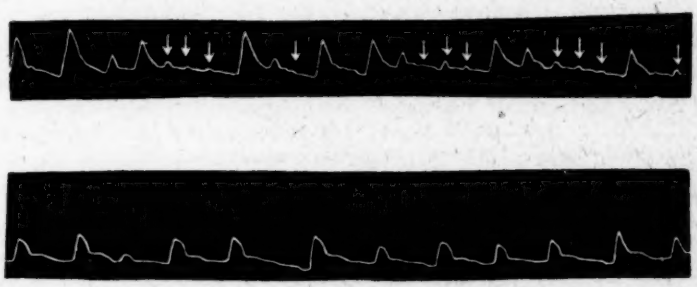


FIG. 2.—Sphygmogram from a case of auricular fibrillation. Upper record, before treatment, showing complete irregularity and a large number of very small pulse waves (marked with arrows). Lower record, after treatment with digitalis, showing greater uniformity in rhythm and form of pulse, all but one of the small ineffective beats having been eliminated. (Reproduced from *The Approach to Cardiology* by permission of Oxford University Press.)

reaches the periphery. Thus the heart rate, as counted with the stethoscope at the apex, is greater than the pulse rate at the wrist, the difference between the two counts being known as the "pulse deficit." The larger the number of ineffective beats the greater is the pulse deficit and the more unproductive work is the heart called upon to perform. It is merely tiring itself out to no purpose. Thus in untreated fibrillation tachycardia is largely responsible for the development of heart failure, the benefit derived from treatment with digitalis being due chiefly to control of the ventricular rate.

Failure to control the tachycardia is usually explained by inadequate dosage. Practitioners are apt to be unduly frightened of digitalis intoxication, which, in my experience, more often results from an excessive maintenance dose given over a prolonged period than from overdosage during the initial stage of digitalization. Patients vary greatly in their tolerance for digitalis, and it is therefore undesirable to use massive doses except in emergency: 3 gr. (0.2 g.) of the powdered leaf given eight-hourly will usually suffice to control the ventricular rate within 24 hours, and thereafter a maintenance dose of 1 to 2 gr. (0.065 to 0.13 g.) generally proves adequate; sometimes even smaller doses suffice. In an emergency 1 mg. of digoxin may be given intravenously.

The most obvious signs of digitalis intoxication are excessive slowing of the heart, nausea, vomiting, and bigeminal heart action, in which every normal beat is followed by an extrasystole. It is important to distinguish between the nausea due to overdosage with digitalis and that due to congestion of the gastric mucous membrane resulting from circulatory stasis in cases of heart failure, since the latter condition is attributable to inadequate control of the tachycardia, which can be relieved only by increasing the dose of digitalis. Likewise, bigeminal heart action is by no means always due to digitalis intoxication, and is not an indication for withdrawing the drug unless it is associated with bradycardia or other toxic manifestations.

When fibrillation is of recent origin, or persists after subtotal thyroidectomy, an attempt should be made to restore normal rhythm with quinidine, 6 gr. (0.4 g.) two-hourly for five doses, repeated if necessary. It is, however, only in those cases in which the disability is attributable to the abnormal rhythm rather than to the associated myocardial or valvular disease that quinidine therapy is indicated. In cases of old-standing heart disease there is a risk of embolism, and the patient is likely to derive more benefit from control of the tachycardia with digitalis.

Auricular Flutter

Flutter is closely related to fibrillation and, like fibrillation, may occur either in paroxysms or as an established condition. It is most often associated with either rheumatic or denegerative heart disease. In this disorder the auricle beats regularly at a rate of about 300 per minute and the ventricle usually responds at half that rate.

Clinically, therefore, auricular flutter may be suspected in cases of regular tachycardia when the pulse rate is in the neighbourhood of 150 per minute, and confirmation may be obtained by noting venous pulsation in the neck at double this rate or slowing of the pulse when pressure is applied to the carotid sinus; but the diagnosis can be established with certainty only by the electrocardiogram, which is distinctive.

Under the influence of digitalis the ventricular rate may be reduced to a quarter of the auricular rate or the heart's action may become irregular, the ventricle responding to every second, third, or fourth auricular impulse. Provided 4:1 heart block is maintained auricular flutter will *per se* cause no appreciable disability, but occasionally a 1:1 ventricular response develops, either spontaneously in untreated cases or in the course of treatment with quinidine, and unless promptly controlled may lead to acute cardiac dilatation.

If a patient with auricular flutter is fully digitalized the flutter will often be converted to fibrillation, and subsequently normal rhythm may supervene. Similarly a transient stage of auricular flutter may be observed before normal rhythm is restored when a patient with auricular fibrillation is treated with quinidine.

Next Refresher Course Article.—"Medical Aspects of Air Travel," by Sir Harold E. Whittingham.

COLLEGE OF GENERAL PRACTITIONERS

Eleven additional general practitioners from different parts of the British Isles have been elected to the Foundation Council of the College. Until the first annual general meeting, to be held in the autumn, the Foundation Council will consist of:

G. F. Abercrombie (London), *Chairman*.
G. O. Barber (Essex).
J. Cottrell (Lincolnshire).
D. G. French (Staffordshire).
Annis C. Gillie (London).
H. K. Glyn Hughes (London).
I. D. Grant (Glasgow).
J. M. Henderson (Perthshire).
W. V. Howells (Glamorgan).
D. M. Hughes (Carmarthen).
J. H. Hunt (London), *Honorary Secretary*.
R. M. S. McConaghey (Devon).
J. G. Ollerenshaw (Yorkshire).
R. J. F. H. Pinsent (Birmingham).
F. M. Rose (Lancashire), *Deputy Chairman*.
Richard Scott (Edinburgh).
J. D. Simpson (Cambridge).
G. Swift (Hampshire).
A. Talbot Rogers (Kent).
G. I. Watson (Surrey).
J. C. Young (Belfast).

Foundation Membership.—By February 12 1,600 general practitioners had joined the College.

Reprints of Steering Committee's Report.—These will be sent to anyone on request.

Plans of Surgeries.—The College is collecting plans and photographs of up-to-date surgeries, consulting-rooms, dispensaries, waiting-rooms, etc. During the past few years many doctors have spent much time and thought in adapting, or building anew, such premises for single or group practices. It is hoped to provide a centre where plans, and perhaps scale-models, of these projects can be collected and studied, so that young doctors may benefit from the experience of others. As this collection grows it will be freely available to any doctors, architects, or builders who may wish to consult it. Will general practitioners who have recently adapted old houses to their practice needs, or who have built new premises, please send to the Secretary (at 14, Black Friars Lane, London, E.C.4) plans and photographs, with a note to indicate the special features of the buildings and of the practices concerned?

CANCER EDUCATION IN CHELSEA

The Borough of Chelsea's Cancer Education Committee held a public meeting on February 17 at Chelsea Town Hall. The meeting was attended by the Mayor of Chelsea, representatives of various interested bodies, and some 200 members of the public. Alderman G. L. TUNBRIDGE presided. He said that the Chelsea Cancer Education Committee had been formed in 1949 when the Borough Council was asked what it was doing about cancer education. Since then the Committee had produced 12 informative leaflets for lay people.

Mr. R. W. RAVEN, F.R.C.S., then gave a brief address in which he described an investigation carried out by the Chelsea Committee with the aid of a questionary. Of the people questioned, 17% believed that cancer is infectious, 27% that it is incurable, and another 20% that it is of doubtful curability; nearly all thought that a careful programme of education would be useful. The object of cancer education, said Mr. Raven, was to substitute knowledge and confidence for ignorance and fear. There were already about 15 cancer education committees at work in Britain, and these should be increased. The population would have to be covered in stages: special attention should be given to teaching district nurses and health visitors—their combined number being nearly 20,000—student nurses, welfare and social workers, who could then disseminate information among lay people. Later a more direct approach by leaflets, lectures, films, and carefully written newspaper articles would be possible. Mr. Raven ended his address by outlining a five-point programme for cancer control.

There then followed a film entitled "Time is Life," and a period for questions. Dr. J. BROWNING ALEXANDER moved the vote of thanks.

FIRST WORLD CONFERENCE ON MEDICAL EDUCATION

LONDON, AUGUST 24-29, 1953

The First World Conference on Medical Education will be held in London at B.M.A. House this year from August 24 to August 29, under the auspices of the World Medical Association. The President is Sir Lionel Whitby and the Deputy President Professor W. Melville Arnott. The first day of the Conference, Friday afternoon, and Saturday morning will be in Plenary Session. Details of the programme are printed below. (A leading article on the Conference appears on page 494.)

Section A: Requirements for Entry into Medical School

Vice-President: Dr. VICTOR JOHNSON, of the Mayo Foundation

Time	Tuesday, August 25	Wednesday, August 26	Thursday, August 27	Friday, August 28
9.45 a.m. to 1 p.m.	General Education in an Age of Science	History of Science Teaching Scientific Method Science is Measurement	Biology Fundamental to Study of Medicine How Much Chemistry and Physics? Introduction to the Social Sciences	Use and Value of Intelligence and Aptitude Tests Method and Value of Interview Examination and Discussion Group
3 to 6 p.m. ..	Requirements for Entry into Medical Schools	Excursion	Selection of Students	Plenary Session

Section B: Aims and Content of the Medical Curriculum

Vice-President: Sir ARCOT MUDALIAR, of the University of Madras

9.45 a.m. to 1 p.m.	Anatomy for the Doctor Physiology for the Doctor Integration of Physiology and Anatomy as a Single Subject in the Curriculum	The Aim of the Medical Curriculum Introductory Clinical Course Teaching Psychological Medicine	Teaching Medicine and Surgery as One Discipline Teaching Minor Surgery The Doctor, the Midwife, and Obstetrics	The Undergraduate and General Practice The Balanced Curriculum
3 to 6 p.m. ..	Pathology—the Basic Clinical Science Pharmacology and the New Therapeutics Medical Statistics and the Design of Experiment	Excursion	Paediatrics a Branch of Medicine The Place of the Specialties in the Curriculum Is an Intern Year Necessary?	Plenary Session

Section C: Techniques and Methods of Medical Education

Vice-President: Dr. A. HURTADO, of the University of San Marcos, Lima

9.45 a.m. to 1 p.m.	The Hospital - bedside Teaching of Medicine Teaching Surgery at the Bedside and in the Theatre Teaching in the Out-patient Department or Polyclinic	Visual Aids in Education One-way Observation Screen The Moving Picture in Medical Education The Still Picture	The Lecture and Group Discussion Medical Education and the Full-time System The Place of the Text-book in Teaching	Methods of Testing Knowledge
3 to 6 p.m. ..	Teaching in the Home The Clinico-pathological Conference The Laboratory in Teaching Experimental Medicine	Excursion	Library and Reference Services The Museum in Teaching The Students' Clinical Society	Plenary Session

Section D: Preventive and Social Medicine

Vice-President: Professor RENÉ SAND, of Brussels

9.45 a.m. to 1 p.m.	Present Status of the Teaching of Preventive and Social Medicine	The Teaching of Epidemiology Demography and Vital Statistics The Teaching of Medical Genetics	The Teaching of Social Psychology Social Environment and Individual Illness The Home Setting in Medical Education	The Teaching of Nutrition Housing Integration of the Teaching of Social Medicine in the Medical Curriculum
3 to 6 p.m. ..	Social Medicine as an Academic Discipline Teaching Social Medicine in the Pre-clinical Period Social Medicine in the Clinical Period The Need for Reorientation of Teaching	Excursion	The Teaching of Occupational Health The Use of Student Health Services in the Education of the Student Infant and Child Care as a Medico-social Problem	Plenary Session

Reports of Societies

HYPOTENSION IN ANAESTHESIA

On February 4 the Sections of Anaesthesia and Surgery of the Royal Society of Medicine discussed "Low Pressure Anaesthesia in Surgery." Professor F. A. R. STAMMERS (Birmingham) was in the chair.

Methonium Compounds

Dr. J. B. WYMAN (London) said that in addition to lowering blood pressure methonium compounds might also protect the patient from shock and prevent established shock from becoming irreversible. At the Westminster Hospital methonium drugs had been used at first only in cases subject to excessive blood loss, or in those in which blood loss impeded the surgeon. Later their use had been extended, and the technique had now been applied in 1,037 operations. He stressed the excellence of the working conditions for the surgeon, the steadiness of the patient's general condition during operation, and the remarkably good recovery afterwards. The patient was protected from trauma as well as from blood loss. The main theoretical objections to hypotension were the risk of dangerously reducing the blood supply to the vital organs and the possibility of vascular accidents. Thrombosis was probably no more liable to occur, and this might be because the linear rate of blood flow was not altered. Cerebral thrombosis had occurred in only one patient, a man with advanced hypertension. There had been two cases of cardiac arrest precipitated by some asphyxia during the operation. However, despite these fatalities, he thought that patients with a cardiac lesion did better than they would with ordinary anaesthesia, and that, once under control, the blood pressure and pulse rate remained remarkably steady. Possibly the damaged heart worked better against decreased peripheral resistance. A patient who had had a previous coronary thrombosis was liable to have another whether or not a methonium compound was used.

Post-operative haematoma was rarely troublesome once the surgeon was accustomed to the technique and tied off all slightly bleeding vessels. Renal complications were few, and the only example of renal failure had been in a patient with Ellis type 1 kidneys, who died two weeks after the operation. Oliguria had occasionally occurred. No major disturbance of liver function had been seen.

Of the five deaths, two were due to the underlying disease and three to faulty technique. A high standard was essential, and the penalties of failure were heavy. Despite his earlier remarks about patients with cardiac lesions doing better, Dr. Wyman mentioned that there might be a depression of the S–T interval in some of the E.C.G. leads for a few days after operation, and that this indicated a certain amount of cardiac ischaemia.

After the operation a head-down position was used for a few hours. He did not recommend the use of methylamphetamine, and he thought that phenylephrine (*U.S.P.*) was in some respects better. Slow recovery of the blood pressure was sometimes due to dehydration and delayed excretion of the hypotensive drug. The difficulties due to prolonged action of methonium compounds might be overcome by the use of "Arfonad (Ro2–2222)," which had a very short-lived effect. From his own experience Dr. Wyman suggested that the future of these drugs might lie as much in the prevention of shock during major surgery as in the provision of an ischaemic field.

Mr. ROBERT COX (London) spoke as a surgeon who had worked with Dr. Wyman and who had no experience of other methods of producing hypotension. The diminished blood loss was sometimes most striking: as examples of blood loss in different operations performed with and without this technique he cited: thyroidectomy 30 and 260 ml., radical mastectomy 32 and 690 ml., prostatectomy 30 and 560 ml., and pelvic evisceration 160 and 1,150 ml. With proper care in general surgery there did not seem to be an increased incidence of reactionary haemorrhage or haematoma formation, and there had been no evidence of an increase in embolism or in renal or hepatic complications. On return to the ward regular blood-pressure readings were taken. Morphine should be given if the patient was restless, otherwise the restoration of blood pressure might be delayed. The extra post-operative attention was compensated for by the lesser need for transfusions. The ward sisters thought that the patients were unusually well after operation, and this opinion was shared by everyone who dealt with the cases.

High Spinal Block

Dr. J. GILLIES (Edinburgh) spoke of high spinal block in which postural adjustment was the main factor in determining the fall in blood pressure and the primary means of restoring it in an emergency. Briefly reviewing the mechanisms involved in the various methods of inducing hypotension, he said that in arteriotomy blood flow and bleeding were reduced more by virtue of the vasoconstrictive response than by the drop in blood pressure. However well controlled, this state came very near to being pathological. Total sympathetic paralysis, by either extradural or subarachnoid block, caused generalized vasodilatation. By appropriate positioning, pooling of blood in dependent parts and a marked degree of hypotension could be achieved. Loss of fluid from the skin ceased during the sympathetic paralysis, and as the motor block did not affect the upper intercostal and phrenic nerves respiration remained spontaneous and a reliable guide to the state of the medulla. In autonomic blockade by methonium compounds the effects were complex, and this might explain why the results were less predictable. Spinal block was a more certain method of producing hypotension for a definite period of time. While all three methods had been used in Edinburgh, he would deal only with a series of 802 operations in which high spinal block had been applied. The patients were poor risks undergoing surgery for vascular diseases, This provided a severe test for a method which in 1946 was considered a reckless procedure. In abdominal surgery high spinal block was chosen as much for its other advantages of muscle relaxation and sensory blockade as for its hypotensive effect, although the latter could be of help in cases where, owing to the nature of the lesion, much bleeding might be expected.

Most of the avoidable mortality had occurred in the first half of the series. Two patients died during operation, one owing to mechanical limitation of pulmonary ventilation and anoxia, the other following a small dose of thiopentone which abolished spontaneous respiration and lowered arterial pressure still further. The few patients who died of cerebral vascular accidents had all had similar trouble in the past, and the technique was now contraindicated in such cases. One patient died of reactionary haemorrhage. There had been three non-fatal reactionary haemorrhages. Seven patients had cerebral vascular accidents (six of these were hypertensives, five of whom had a previous history of such trouble). There was only one case of coronary thrombosis with cardiac arrest in a patient with previous angina. Cardiac arrest occurred in one other patient as a result of asphyxia. Immediate cardiac massage was successful in both cases. Oliguria was noted in three patients, a figure which was in no way significant. A low head of pressure to the kidney did not seem to matter so long as there was vasodilatation and an undiminished volume flow. Post-operative ischaemia of the limbs occurred in 7 of 222 lumbar sympathectomies, and one limb was lost.

In 782 patients with no severe pre-operative cerebral vascular episode only two had developed such troubles

later, whereas in 20 with a history of severe cerebral accident before operation 9 developed them later. Similarly in 784 patients without severe myocardial disease there was no subsequent coronary thrombosis, whereas in 18 patients with severe myocardial damage there was one post-operative coronary thrombosis. Spinal cord damage occurred in two others, and this was a serious matter. In expert hands, however, this complication should reach a low irreducible minimum.

Contraindications to inducing hypotension were (1) myocardial disease; (2) arteriosclerosis, whether local or generalized; (3) a history of previous cerebral vascular accident; (4) anaemia, chronic pulmonary disease, congestive heart failure, and other conditions affecting oxygen transport; and (5) malignant hypertension. The *only indication* for hypotension was when its advantages to the patient and the surgeon were definite and were likely to outweigh the accepted risks.

Discussion

Mr. GEOFFREY PARKER (London) said he had been prejudiced against the use of methonium compounds at first, but was now happier about them. The bloodless field made it wonderfully easy to demonstrate all the steps in an operation such as prostatectomy. Dr. C. T. BARRY (Edinburgh) said that with methonium compounds he had had 8 deaths in 212 cases. He thought a high spinal was more reliable. Four of his eight fatalities had been due to severe paralytic ileus. Dr. R. F. WOOLMER (Bristol) said that vasoconstriction was Nature's way of combating shock, and yet the opening speaker had advocated methonium in the treatment of established shock. He thought that the exponents of this method were confusing "shock-shielding" with "shock-hiding." Dr. M. H. A. DAVISON (Newcastle), after considerable experience, had abandoned the methonium drugs. He pointed out that the opening speakers had recorded three deaths on the table in less than 2,000 cases, whereas there had been only one such death in the last 60,000 cases at his hospital. He emphasized, too, the very real risk of cerebral damage in many cases. Dr. A. R. HUNTER (Manchester) described the limited use of hexamethonium in neurosurgery, chiefly to make the impossible possible. The method was mainly of value with angiomas, aneurysms, and vascular meningiomas. Some patients had prolonged hypotension, and a few had shown intolerance by developing venous congestion in the operative field. There was also a significant increase in post-operative vomiting. Dr. P. R. BROMAGE (Chichester) said that in the presence of complete afferent blockade from the operation site eosinophil counts suggested that the adrenocortical response was delayed until the effects of the block had worn off. In the arteriosclerotic subject the electroencephalogram showed delayed return of normal alpha rhythm after profound hypotension.

Dr. GILLIES, in reply to a question by Mr. N. E. Tanner on whether the induction of hypotension was indicated in the surgery of portal hypertension, said that he did not consider the method suitable. The hazards of bleeding in such patients were great. With reference to Dr. Barry's remarks on paralytic ileus, he quoted a personal communication from Dr. F. Holmes at Edinburgh, reporting 19 non-fatal cases of paralytic ileus in 155 orthopaedic operations (mostly on the hip) in which hexamethonium had been used. Dr. Davison's emphasis on possible cerebral damage was important, although Nilsson's observations were on few cases and all effects were transient. With spinal block anything above 10 degrees head-up must be considered dangerous. The head-down position should never be much below horizontal, otherwise a dangerous congestion might ensue.

Dr. WYMAN congratulated Dr. Davison on his long series of cases without a death on the table. He felt, however, that such events were largely unpredictable and that such a satisfactory experience could be purely due to chance. Contrary to Dr. Bromage, he thought that there was a normal eosinophil response to operation.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Smoking and Lung Cancer

SIR,—It would seem, according to some of the critics of our conclusion that "tobacco smoking is a factor in the production of carcinoma of the lung" (for example, Professor R. D. Passey, February 14, p. 399), that we ourselves based that conclusion in part—and even largely—upon the observation that over the last 50 years cigarette smoking and the recorded mortality from lung cancer have risen together. In fact our conclusion is based upon evidence that is *entirely* independent of that time correlation. The time correlation was, of course, our starting point—it suggested that smoking was a factor worth investigating. But having applied that stimulus it ceased to have any interest whatever for us until our epidemiological inquiry was over and had *alone* led us to the conclusion we have quoted above.

That epidemiological approach and the results it gave are also, perhaps, being underestimated by Professor Passey and others. In drawing our conclusions we were not dealing with a handful of uncontrolled patients, nor making light-hearted suggestions, such as those he quotes about breast cancer and Edwardian corsets, based upon a few clinical impressions and a vivid imagination. We set about a most carefully designed survey, a survey that took in, all told, nearly 5,000 patients, was carried out in Greater London and four provincial cities, and occupied nearly five years. Evidence based on 1,465 lung cancer patients and 1,465 carefully matched controls does, we submit, carry some weight. In view, however, of the emphasis that has been placed, quite wrongly in our view, upon the correlation in time we might perhaps remind the reader briefly of the salient features of that survey. We have endeavoured to bring all its important results together in one single table, given below (for details of the absolute numbers, which vary according to the items, and for technical tests of significance, etc., the reader must see Doll and Hill (*British Medical Journal*, December 13, 1952, p. 1271).

The Proportion of Patients Interviewed who were Noted to have Given Characteristics

Section A. Equalities

	Characteristic	Carcinoma of the Lung Patients	Control Patients
1	Sex	Equalized in design of observations.	
2	Age		
3	Places of interview (5 areas)		
4	Occupations	No significant difference in 74 out of 76 categories.*	
5	Social class (males) number falling in classes I and II	15%	17%
	Social class (males) number falling in class V	17%	16%
6	Number with previous residence near a gas works	23%	22%
7	Number with different forms of heating in living room for 30+ years:		
	Coal fire	86%	85%
	Gas fire	1·6%	2·2%
8	Number with previous history of asthma, chronic nasal catarrh, pleural effusion, or pulmonary tuberculosis	17%	15%
9	Regular users of petrol lighters	43%	41%
10	Number of smokers who said they inhaled	65%	67%
11	Smokers of mainly hand-rolled cigarettes	21%	19%
12	Users of one of 4 main named brands of cigarettes	57%	57%
	Users of mixed brands	34%	32%
	Regular users at some period of Turkish cigarettes	4%	5%
13	Number of male snuff-takers, occasionally or regularly	3%	4%
14	Number of non-smokers amongst women in the provinces	57%	57%

* In two occupational groups—miners and policemen—there was a relative deficiency of cancer cases.

Observed Proportions of Patients with Given Characteristics

Section B. Inequalities

	Characteristic	Carcinoma of the Lung Patients	Control Patients
1	Number of men who were non-smokers:		
	Greater London, 1948–9	0·3%	4·2%
	Greater London, 1950–1	1·0%	4·2%
	Bristol, Cambridge, Leeds	1·3%	4·4%
	Newcastle	0·0%	5·3%
2	Number of women who were non-smokers:		
	Greater London	30%	54%
3	Number of men smoking 25 cigarettes or more daily (or the equivalent in pipe tobacco):		
	Greater London, 1948–9	26%	13%
	Greater London, 1950–1	26%	16%
	Bristol, Cambridge, Leeds	24%	11%
	Newcastle	21%	12%
4	Number of women smoking 25 cigarettes or more daily:		
	All areas	11%	1%
5	Number who started smoking before the age of 20:		
	Men	80%	77%
	Women	29%	24%
6	Number who had given up smoking for more than 10 years:		
	Men	1%	4%
	Women	1%	4%
7	Number of male smokers who, as a rule, smoked cigarettes only	74%	69%
	Number of male smokers who, as a rule, smoked pipes only	4%	7%
8	Number of male cigarette smokers who had used cigarette holders occasionally or regularly	5%	12%
9	Number of males who had chewed tobacco occasionally or regularly	3%	5%
10	Number of men aged 45–74 smoking 25 cigarettes or more daily (standardized rate):		
	Patients with carcinoma of the lung	24%	
	Patients wrongly diagnosed as lung cancer		11%
	Patients with other respiratory diseases		11%
	Patients with other forms of cancer		13%
	Patients with other diseases		14%
11	Number with previous history of:		
	Chronic bronchitis	17%	11%
	Pneumonia	17%	10%

In the upper part of the table, Section A, we set out the principal characteristics in which our carcinoma of the lung group did *not* differ appreciably from the control patients—that is, those patients whom we took into the inquiry as a standard of comparison. To limit the possible variables, the design of our survey deliberately made them equal in sex, age, place of interview, and, largely, in hospital of admission. It will be seen that they have also revealed themselves to be remarkably alike in other characteristics—their social class and their occupations, their residence near a gas works, their heating in the home, their previous history of certain respiratory diseases. In relation to smoking they do not differ in their use of petrol lighters, of hand-rolled cigarettes, of different brands of cigarettes; they do not differ in the habit of inhaling. With these striking equalities—particularly in some aspects of smoking—it would seem to us to be unreasonable to argue that either our controls or our cases are biased, and therefore not comparable, or that the information given by the two groups is not equally reliable.

How, then, can we explain the picture given by Section B of our table? Here we have brought together the various ways in which the carcinoma of the lung patients *do*, as a group, differ from the control patients. They include significantly fewer non-smokers and a marked excess of relatively heavy smokers in both sexes, with, in men, a consistency in time and space that is striking; they include more persons who started smoking earlier in life and fewer who have given up; they include relatively more cigarette smokers and fewer pipe smokers; they include fewer users of cigarette-holders and fewer chewers of tobacco. In short, broadly speaking, they differ radically in the *amount* of tobacco they have smoked, and they differ, it seems probable, in the *way* they have smoked. Other groups of patients do not reveal this difference in the amount smoked—including, be it noted, a group originally, but wrongly, diagnosed as carcinoma of the lung. It is the privilege of the lung cancer group to be so marked. The only exception lies in the equality of non-smokers amongst the few women we observed in the provinces (as shown in Section A).

The two groups are also different, Section B shows, in their previous history of chronic bronchitis and pneumonia. We give reasons in our paper for supposing that this comparison may be fallacious, though we do not wholly dismiss it. Chronic bronchitis is held by many to be related to smoking. There is also some evidence (not included in the Table) that the carcinoma patients had passed more of their lives in urban areas, which is consistent with Stocks's work on the urban/rural incidence rates. Basically, then, it is the contrast between Section A and Section B of our Table that leads us to the belief that tobacco smoking is of aetiological importance in lung cancer.

This evidence, we repeat, is quite independent of the time correlation. No critic has offered any alternative explanation of it that carries conviction—and indeed the only one that has been put forward at all is that subjects with a particular constitution may be prone both to smoking heavily and to carcinoma of the lung. We have put forward our own interpretation and belief—that the figures simply mean what they show.

Professor Passey and Dr. Gallop ask, If the reported increase in lung cancer is due to tobacco smoke, how does it come about that there is no increase in the incidence of cancer in other parts of the respiratory tract, such as mouth, tongue, and pharynx, which suffer a greater exposure to the smoke and for a longer time? There are, however, analogies for such events, however curious they may appear to be. For instance, in nickel refining in South Wales it is well known that some undetermined carcinogenic agent, acting in the first quarter of the present century, produced a gross excess of cancer in two sites, and two sites only—the ethmoid and the lung. Why not the mouth, the tongue, and the pharynx? Similarly, no excess in any site but the lung has followed the exposure of the Schneeberg miners. A declining cancer rate in the buccal cavity is, in fact, consistent with the hypothesis put forward by some that cancer in these sites is related to the prevalence of pipe-smoking.

We made perfectly clear in our paper that we did not believe that *all* cases of lung cancer were due to smoking—indeed, we called that a most unlikely event and pointed out that we had observed certain cases who had never smoked. One of us (R. D.) has, indeed, elsewhere attempted to calculate from our data the death rates of men and women non-smokers, and on the assumptions made those death rates did not differ materially (Milroy lectures, in the press). We need hardly point out that with *far* more women than men non-smokers in the population a relatively greater proportion of deaths in women must be of non-smokers—though their death rate among them might still be negligible. The difference in past tobacco consumption between the sexes is, it appears to us, quite capable of providing the main explanation of the present sex ratio of mortality. Trade statistics show that of the total tobacco consumption of the country 25 years ago only 2.5% was smoked by women. We do not believe that Dr. Shera need invoke sex hormones as a factor.

Professor Passey suggests that the only "satisfactory solution of the problem would be the study of a large group of smokers in comparison with an equally large group of non-smokers." This we are endeavouring to make in our observations of the mortality amongst those doctors who told us their smoking habits some 15 months ago—but we hardly like to appear impatient.

Finally, he asserts that "when doctors disagree it is bad for the patient." We might remind him that in the past they often have disagreed. They disagreed when Lord Lister endeavoured to introduce antiseptic measures. It *was* bad for the patient. Quite often he died.—We are, etc.,

RICHARD DOLL.
A. BRADFORD HILL.

London, W.C.1.

SIR,—There are certain points in the letter of Professor R. D. Passey (February 14, p. 399) which I feel require some comment. Professor Passey suggests that the "immeasurably greater degree" of ability to diagnose cancer of the lung is as closely related to the increase in lung cancer as between cigarette smoking and the increase of lung cancer. Surely Professor Passey cannot seriously suggest that in the past 10 years the ability of medical practitioners to diagnose cancer of the lung as a cause of death has markedly changed. If there was some social reason for the increase in the number of certifications—that is, reluctance of doctors to certify cancer as a cause of death—then this should be reflected in the certifications of death of all other forms of cancer. Deaths from cancer of the trachea and bronchus have risen from 4,815 in 1940 to 11,241 in 1950, an increase of 133%. Certified deaths from cancer of the large intestine have risen only from 9,809 in 1940 to 10,153 in 1950. This trifling increase of 3.5% would seem to dispose of the idea that there has been any marked increase in the *x*-ray diagnostic facilities. The second point was that no carcinogen had yet been found in tobacco smoke, but it was stated in Professor Bradford Hill's article that carcinogen has been demonstrated in tobacco tar.

A mere correlation in time between the increase of tobacco smoke and cancer of the lung would indeed be a highly fallacious premise on which to base any argument as to the aetiology of the one against the other, but what the survey shows is that a much larger number of persons who suffer with cancer of the lung smoke cigarettes than would be accounted for by chance. It is certainly true that in the past many theories as to the causation of carcinoma have been proved false by later experiment, but a statistical survey of this type is one of the most potent methods of distinguishing facts from fancy—that is, in the demonstration that residence near a gas works is of no import and the non-carcinogenic properties of the cigarette lighter.

Finally, Professor Passey states that we do not know how many of the 68 women smokers who suffer with carcinoma would, in fact, have suffered from this disease had they not smoked, but, applying the figures of relative risk in table XII, it would appear that this figure would have been under 10. Professor Bradford Hill's article may not have proved that carcinoma of the lung is caused by tobacco smoking, but it has put the matter in so grave a doubt that any reasonable person would need to receive very strong weight of evidence before dismissing the matter as of no account. No single survey, even one so carefully planned and carried out, could be said to prove so important a subject, but it certainly does make it of the utmost importance that further research be pressed forward with the greatest celerity.—I am, etc.,

London, W.8. H. BINYSH.

SIR,—Your publication of "A Study of the Aetiology of Carcinoma of the Lung," by Dr. R. Doll and Professor Bradford Hill (December 13, 1952, p. 1271), which was followed by a television programme on smoking, and much Press publicity, including front-page banner headlines in at least one daily paper, have resulted in great and justifiable public alarm about the ill-effects of smoking. A conference has been hurriedly called for the purpose of planning further and more extensive research on this subject. Let us have this, by all means. Let us make assurance doubly sure. But extensive research, well planned and carried out, is extremely time-consuming, and must not be made an excuse for our neglecting to take immediate steps to safeguard the public from this grave and rapidly increasing malady.

Your leading article (December 13, 1952, p. 1299) implied that the association between smoking and cancer of the lung was virtually proved, in so far as statistics can prove anything. The second limb of Doll and Hill's investigation confirmed the conclusions of their first, and the whole confirmed those of Wynder and Graham,[1] and of other investigators. A long-nurtured suspicion, born of extensive clinical observation, has thus been subjected to repeated large-scale investigations by independent investigators of high standing, and has been shown to be well founded. Its validity is therefore proved beyond all reasonable doubt, although I appreciate that many smokers are, understandably, not reasonable when there is a threat to their supplies of tobacco, and are certain to cast doubts, including "phony" ones, on the validity of such utterly unacceptable findings. But this should not be allowed to deter or delay us in the performance of our duty, which is clearly to call on the nation to stop smoking now, voluntarily in the first instance. I realize that the psychological and financial repercussions would be enormous. But even more enormous, in my view, would be the upsurge in the national health and morale. Tobacco smoking is a disease in its own right—a drug addiction—and well worth curing even if it did not predispose to any other affection.—I am, etc.,

Wallasey. LENNOX JOHNSTON.

REFERENCE

[1] *J. Amer. med. Ass.*, 1950, 143, 329.

"A Thorough Overhaul"

SIR,—We in this partnership are concerned over the increasing number of requests we have from National Health Service patients for a "thorough overhaul," or, as they frequently put it, a "medical." While we agree with the desirability of this and have not as yet turned any such requests down, we are getting a little apprehensive at the increasing frequency of these requests, due, we have no doubt, to the many health articles in the popular magazines and the sometimes horrifying programmes on the radio and television. This is certainly going to become an acute problem, because, if such examinations are not done as thoroughly as those for life assurance purposes, they are not only useless but may be dangerous.

We should like to ventilate this question and ask how our colleagues elsewhere deal with it.—We are, etc.,

RONALD COLDREY. G. A. F. QUINNELL.
D. R. W. BURBURY. G. E. P. KELLY.

Teignmouth.

The College of General Practitioners

SIR,—It is evident from the letter of Drs. J. P. Denny, C. H. Highfield, D. L. Isaac, and A. Murphy (February 7, p. 333) that my previous communication (January 24, p. 219) has been misunderstood. In order to eradicate any false impressions, I would be grateful for the opportunity to answer a few of the points which they make.

First, it is not quite fair to speak of a *fait accompli* being presented to the profession. The steering committee has considered the views offered to it by members of the profession, and Dr. Denny and his co-writers had every opportunity to submit theirs. The committee has now gone a stage further and made some *provisional* arrangements for the establishment of the College and has given it a *provisional* constitution. In its report it makes it quite clear that a general meeting will be held in 1953, at which a new council will be elected by the full body of members, the provisional constitution will be reviewed, and the by-laws will be submitted for amendment and confirmation. A second general meeting will be held in 1954, when the same procedure will be followed. Such an arrangement can hardly be called undemocratic.

The fact that more than 1,500 general practitioners have joined the new college in its first five weeks has shown indisputably that there is a real need for it. Those who have not yet enrolled are not necessarily opposed, and many, I am informed, are still joining daily. This degree of support from practitioners immediately after the birth

of their college, with its enthusiastic reception from many other quarters, has been far more encouraging than even its most ardent supporters had expected.

The steering committee clearly states in its report that the new college is for *all* general practitioners who care to join it. None are excluded, and it is quite untrue to state, as Dr. Denny and his colleagues have done, that the college is only for a few enthusiasts and not for all. Furthermore, it is not one of the aims of the college to "dispense distinctions" under its present constitution. If eventually it is decided to institute a diploma, it will be for the profession as a whole to accord it the value which it deserves.

The B.M.A. has, I believe, welcomed this venture and recognizes the college as a body complementary, and not antagonistic, to itself. This should allay any fears that a new negotiating body has arisen to interfere with existing work in this field.

After three years the Royal College of Obstetricians and Gynaecologists had 276 members; after five years the American Academy of General Practice, a highly successful and useful organization, had enrolled 15% of the general practitioners of the United States; in its first five *weeks* our new College of General Practitioners has made a truly remarkable start, and its future success is assured.—I am, etc.,

Sheffield. H. H. PILLING.

SIR,—I much appreciate the kind reference of Dr. J. P. Denny and others (February 7, p. 333) to my letter (January 24, p. 218) and want to dispel some doubts expressed about my meaning. Regarding the increasing deterioration of the status of general practice in the past decade, the profession will welcome from the College of General Practitioners any help in our attempts to "stop the slide." I did not venture the opinion that the college was necessary in addition to existing efforts; but the exigency presents a great opportunity for the new college to show its mettle.

Is the doctor's prestige, *vis à vis* his specialist confrères, synonymous with worth, as my correspondents assume? Prestige means influential status judged by worldly standards, and it is the fall of this that we lament. Whereas the sustained concurrent efforts of doctors to serve their patients' vital needs despite degrading conditions enhance our esteem for their worth—moral or academic. But, "trying to cope," they are losing touch seriously with the specialists. Consultations are fewer; at those in the patient's home the absence of the general practitioner is often accepted; patients are commonly introduced to the out-patient clinic with but scrappy notes. Scamped procedure is foreign to healing. It also impresses the public unfavourably. A cold formality is supplanting the good fellowship that made a consultation an event in pre-war practice. *Spiritus intus alit*. Not only was discussion stimulating but, writing from personal experience, the young consultant gained much from the shrewd dicta of the family doctor and his way of handling the patient. Incidentally, the quiet decorum of the occasion inculcated respect among patient and relatives.

When the consultant-general-practitioner bond weakens, the doctor's prestige—within his profession, too—diminishes. I tried to emphasize in my letter how indispensable the directive influence of the general practitioner has become for the patient to derive full benefit from the cluster of specialists now available in the N.H.S. The family doctor should not only invoke but also co-ordinate their services and play the nuclear role in the clinical cell. It is our duty among our clientele to acclaim him *primus inter pares*. The warning words of Dr. F. H. Young in his address on pulmonary tuberculosis (February 7, p. 287) illustrate how needful this function is. Unless the general practitioner is in charge, the patient is apt to fall between two stools—medicine and surgery—and "the best laid schemes o' mice and men gang aft a-gley."

Let the profession give due prominence to this major responsibility of the general practitioner. Such a signal from the "technicians" is due to convince both the public and the Ministry of Health that the bad conditions in general practice are converting the patient's "guide, philosopher, and friend" into a health "official."—I am, etc.,

Bristol. A. WILFRID ADAMS.

Acute Labyrinthitis

SIR,—In reference to the article by Dr. W. L. Burrowes on "Acute Labyrinthitis" (November 29, 1952, p. 1182), we have during the last year seen many cases of labyrinthitis, although most have not been as severe as those reported. The attacks were frequently associated with other symptoms of influenza, and we feel that, when it occurs alone, the labyrinthitis is possibly caused by an influenza virus of low virulence.

With respect to treatment, we added potassium iodide 3 gr. (0.2 g.) to a simple sedative mixture such as the following: ammon. brom. 3 gr. (0.2 g.), sodii brom. 3 gr. (0.2 g.), tinct. nux vom. 4 min. (0.24 ml.), sp. chloroform. 10 min. (0.6 ml.), inf. gent. co. ad ½ oz. (15 g.). Patients will often be improved within 24 hours even in quite severe cases.—We are, etc.,

JOHN MALCOLM.
Burwood, Australia. SYDNEY L. CHURCHWARD.

Malignancy in Undescended Testis

SIR,—Mr. Eric Coldrey's case of malignant tumour in an undescended testis (February 7, p. 335) is remarkable not only for the extraordinary size of the growth but also for the association with a marked degree of hypospadias. Since the earliest times of cancer research the frequency of association between developmental disturbances and malignancy has been observed and has given rise to various theories on cancer origin. I myself investigated a case of evolutionary anomaly connected with carcinoma which may be worth recording, particularly, as Mr. Coldrey says, as malignant changes with imperfect migration of the testis are very uncommon.

A woman aged 30 was admitted to a gynaecological clinic in a state of complete unconsciousness. A prominent malignant tumour was located in the right inguinal area, spreading considerably. It was inoperable. The patient had always been in good health, but had never had a period. Her body was well proportioned and completely female, with excellently formed breasts and female hair distribution. Only the axillary region was hairless. On examination, however, I found complete absence of a uterus, the vagina ending blindly. From this syndrome I made a diagnosis of error of sex and cancer of a cryptorchic testis in a case of male pseudohermaphroditism. The patient died four days later, and the findings at necropsy confirmed the diagnosis. The patient had never had a doubt of being a woman. The anomaly must have started at an extraordinarily early stage of embryonic life, resulting in such a complete form of pseudohermaphroditism accompanied by the secretion of oestrogen quite excessive in a male.—I am, etc.,

London, N.W.3. HANS BAB.

The General Practitioner and Mass Radiography

SIR,—Dr. F. A. Nash, Mr. B. Benjamin, and Dr. T. J. Lee describe (February 7, p. 304) the facilities offered to general practitioners by the South-west London Mass *X*-ray Service. This was the subject of favourable comments in your annotation (p. 322). I would like to add my appreciation of the above article and say how experience in Newcastle-upon-Tyne has shown that rapid *x*-ray facilities of this kind are greatly appreciated. Such a scheme has been in operation in Newcastle-upon-Tyne since 1944. The following Table gives some particulars of this. It will be seen that the numbers of doctors' patients attending have risen considerably since the scheme started.

Dr. W. H. Dickinson, the first medical director of this mass *x*-ray unit, was responsible for the inception of the scheme; I have only continued the work since his retirement in April, 1952. At first practitioners were requested to send a note with the patient, and a printed letter form

Year	Total Attending	Recalled for 2nd Examination	Requiring Investigation or Observation
1944	754	196	45 or 6%
1946	457	25	65 „ 14·5%
1947	348	54	25 „ 7%
1948	2,625	570	238 „ 9%
1949	1,985	385	119 „ 6%
1950	3,486	601	236 „ 6·5%
1951	4,503	793	313 „ 7%
1952	6,959	842	516 „ 7·5%

was sent back to the general practitioner. Now they are supplied with cards and envelopes, and the report upon the miniature film is typed or stamped upon the card, which goes back to the general practitioner. No elaborate analysis of the patients' symptoms has been kept. In 1949, 44 cases referred by general practitioners were found to have active pulmonary tuberculosis, in 1950 81, and in 1951 86, giving an average of 2% compared with 0.2% from routine *x* rays done in the unit. With the consent and approval of the general practitioner concerned, patients with other abnormal shadows, including probable cardiac lesions or conditions other than tuberculous, were referred to the cardiovascular department or the thoracic unit in the Newcastle General Hospital, where the mass radiography unit is based.

As the mass radiography unit is mobile, the amount of general-practitioner work is affected by the amount of time that it is away from its base, but when it is not away special sessions are arranged on one afternoon and evening per week for general practitioners' cases.—I am, etc.,

Newcastle-upon-Tyne. GEORGE HURRELL.

SIR,—Your annotation on "The G.P. and Mass Radiography" (February 7, p. 322) seemed to attribute to us the suggestion that all mass *x*-ray units should concentrate entirely on the examination of minor symptom cases sent by doctors. We did not express any views about the uses to which existing mass *x*-ray units *should* be put. We did estimate that a comprehensive general-practitioner *x*-ray service *could* be provided if the units in large towns concentrated entirely on such cases. In fact, we are in agreement with your annotator's views on the importance of the other duties of the mass *x*-ray teams. The question of the relative values of different methods of using these units is an important and separate issue, but we did not deal with it in our paper (February 7, p. 304).

Since our paper was written the South-west London Mass *X*-ray Centre has been opened to provide for the needs of general practitioners. This centre now serves 400 doctors, who are sending 200–300 patients a day for examination. This increase in referrals by general practitioners at a time when they are immensely busy indicates that they value the service.—We are, etc.,

F. A. NASH.
B. BENJAMIN.
T. J. LEE.

London, S.W.17.

Measurement of Tissue Components Radiologically

SIR,—We are pleased to learn from the letters of Dr. E. A. Miskin and Dr. Frank Falkner and Miss Sylvia Wisdom (January 31, p. 275) that some consideration had been given to the geometry of their tube-shift technique, although withheld from the original publication. We wonder, however, if Dr. Miskin, Dr. Falkner, and Miss Wisdom are agreed as to the scope and limitation of the method, for whilst Dr. Falkner and Miss Wisdom write: "Our method is intended for measurement of tissues in such parts of limbs as the upper arm, calf, thigh, etc., in both infant and adult," Dr. Miskin writes: "In the method as applied, and as recommended for *child* study . . ." We have never denied that the shift method may be mathematically accurate for children's calves, but with limbs of diameters up to, say, 6 cm. an anode film distance of only 120 cm. may be regarded as teleradiography with an error of less than 3%.

We were misquoted as recommending an exposure of 1 second at 15 mA in radiographing infants. This was not our intention. However, should we be asked for a practical solution, an exposure of ¼–½ second at 15 mA with an anode film distance of 120 cm. would be a suitable starting point for the smaller patients with whom short exposures are necessary. This compromise (which has been tested in our departments) is put forward as but one of many alternatives, as it is not possible to discuss this subject at length in these columns. The advantages of this method are: (1) only one 15 mA apparatus is required; (2) the exposure time is the minimum these sets will allow; (3) errors due to focal spot size, photographic quality, motional blurring, measurement of tube-shift and anode film distance, subjective errors and calliper errors are far less important; and (4) tissue proportions can be read directly from a normal film rather than calculated indirectly from a film which looks like Clapham Junction in a fog.—We are, etc.,

B. C. H. WARD.
G. N. WEBER.

London, S.E.3.

Effect of Isoniazid on Glucose Tolerance Tests

SIR,—In view of the figures published by Dr. G. R. W. N. Luntz and Mr. S. G. Smith (February 7, p. 296) of the effect of isoniazid on glucose tolerance tests, the attached small series may be of interest.

Between April and June, 1952, six non-diabetic patients suffering from active bilateral pulmonary tuberculosis—Case 3 also had a gastro-enterostomy—received isoniazid in doses of 200–250 mg. daily. At first this was given in 50-mg. doses distributed throughout the 24 hours, but later in doses of 100–150 mg. twice daily. Plasma levels of isoniazid were not determined. Blood sugar estimations (Folin and Wu) were carried out in the fasting condition and one hour after the ingestion of 50 g. of glucose before isoniazid therapy was started, and thereafter at weekly intervals. The series is thus comparable with Dr. Luntz's controls.

Case		Blood Sugar in mg./100 ml.					
		Before Isoniazid	Weeks after Isoniazid				
			1	2	3	4	5
1	Fasting	86	96	77	88	88	64
	1 hr. after glucose ..	148	124	91	112	104	76
2	Fasting	82	104	108	73	92	
	1 hr. after glucose ..	136	120	145	86	96	
3	Fasting	116	108	108	96	84	
	1 hr. after glucose ..	192	128	144	224	136	
4	Fasting	96	92	105	77	84	
	1 hr. after glucose ..	104	120	140	69	112	
5	Fasting	64	68	60	88	64	
	1 hr. after glucose ..	96	88	84	96	80	
6	Fasting	80	68				
	1 hr. after glucose ..	120	132				

We draw no conclusions from this small series, but the results do not appear to confirm Dr. Luntz's findings of raised blood sugar levels in non-diabetics receiving isoniazid.—We are, etc.,

J. A. KEEPING.
M. W. HUTCHINGS.

London, W.10.

School Dental Service

SIR,—Dr. F. G. Hardman (February 14, p. 401) cannot see why dental nurses should be considered a menace. The dental profession is happy to employ auxiliaries in the shape of technicians, receptionists, secretaries, surgery assistants, and oral hygienists. It objects to a new type of auxiliary who will perform surgical operations on living tissues. The analogy with nurses and the medical profession is false. Nurses do not normally administer anaesthetics, perform minor surgery, or use local analgesia, with or without supervision.

The dental profession still has "Dentists 1878" on the Register, and nearly 30% of its ranks are "Dentists 1921." It is liable to have "Dentists 1953" in service until A.D. 2028, even if the so-called "experiment" is judged a failure.—I am, etc.,

Birmingham. C. N. JEFFRIES.

Kindness to Patients

SIR,—I read with great interest your leading article (January 31, p. 264) and the letter from Dr. Guy Roworth (p. 271) explaining his valuable idea of having a leaflet in the wards. I suggest, however, that, in addition, "conditioning" of the patients should start before they enter the hospital, and for this purpose I sent a leaflet some time ago to the King's Fund in the hope that hospitals would send it out with the card of admission. This leaflet sought to explain the domestic details and relationships which exist in the life of a hospital ward and to simplify the details of routine which sometimes cause anxiety at first to new patients. I understand it was turned down by the nursing committee.—I am, etc.,

York. MALCOLM DONALDSON.

Surgery of the Heart

SIR,—You gave us a very kind and good leading article (February 14, p. 383) on our recent follow-up of 200 patients with morbus caeruleus (p. 349).

Your comment that we said nothing about similar patients with direct operations might be interpreted as disapproval of Mr. Brock's operation. We should, perhaps, have concluded our paper by saying that we are hoping to produce a similar follow-up in the very near future of the patients who have had valvotomy and infundibular resection, but these operations started about a year later, and we wanted the follow-ups to be as comparable as possible.—We are, etc.,

MAURICE CAMPBELL.
D. C. DEUCHAR.

London, S.E.1.

Intercourse after Syphilis

SIR,—Your expert, in his reply (February 7, p. 348) to the comments of Dr. P. A. Clements and Dr. T. E. Osmond on his original reply to a question (January 10, p. 115), does not seem to have been very fortunate in his choice of Pariser[1] for support of his contention that *S. pallida* is not found in the semen of an uncured syphilitic person. Study of Pariser's paper inclines one strongly to agree with the criticism of it by that very sane syphilologist, Dr. Joseph V. Klauder, who is reported at the end of Pariser's paper as having said in the discussion thereof:

"Unfortunately these studies do not offer a laboratory test to discover when the seminal fluid no longer harbors the organism. Fournier showed some years ago that the seminal fluid may transmit the disease before the appearance of the chancre. I recently observed a patient with an extra-genital chancre, there were no lesions on the genitalia. He infected his wife through the seminal fluid, since she presented a chancre of the cervix soon after the appearance of her husband's extra-genital chancre. If Dr. Pariser continues his studies I would suggest that he concentrate pooled specimens of seminal fluid from the same patient by partial evaporation in order to inject the entire residue into a rabbit's testicle."

But why does your expert rely, as apparently he does, on the alleged absence of *S. pallida* from the pure semen as secreted in the testicle? What does it matter whether the fluid emitted in sexual intercourse picked up *S. pallida* in the testicle or in the urogenital canal? Does your expert think that seminal fluid could infect only through the ovum? This question of the precautions that are necessary after treatment for early syphilis is highly important. It is all very well to be optimistic when the penalty of mistaken judgment is not borne by the expert, but for the kind of people who matter to the country a syphilitic infection is psychologically, if not physically, a life sentence, and I suggest one should be sure of one's facts before airily telling a syphilitic patient that he can do something which might pass the disease to his consort. Proof of a negative in this matter demands most scrupulous and exacting tests, and, until we have evidence that early syphilis is *always* eradicated by the usually prescribed course, the precautions and the after-treatment observation should be as severe as they ever were.—I am, etc.,

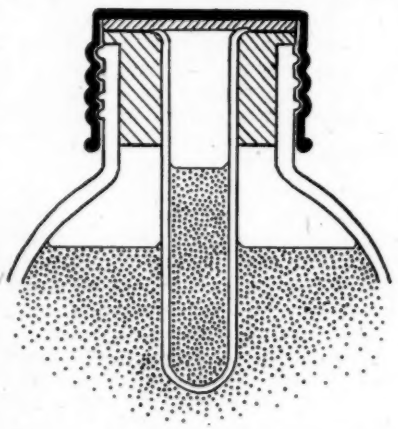
London, S.W.1. L. W. HARRISON.

REFERENCE

[1] *J. Invest. Derm.*, 1942, **5**, 311.

"Pilot" Tube for Bottles of Blood

SIR,—From time to time there is discussion in hospitals about the wastage of donor blood. It has been pointed out that the practice of cross-matching bottles of blood which are not subsequently needed can be made less wasteful if each bottle is accompanied by a "pilot" tube of the same blood, so that the main bottle need not be opened until it is actually needed. Two chief objections to this practice are made—that study of films to exclude the presence of organisms in the blood must be made with the blood in the bottle itself, and that a pilot tube may be detached from its parent bottle or wrongly labelled.



To the first of these objections there is no answer, except that there are few laboratories where routine tests for infected blood are made. The second objection can be met by a method of incorporating the pilot tube in the bottle. I have devised a method which does not necessitate any alteration in the existing bottles. In place of the flat rubber disk covered by the aluminium cap at present used, a deep rubber stopper with an upper flange closes the neck of the bottle. Through an opening in this stopper a 10-ml. test tube fits tightly so that its top is flush with the top of the stopper. After the bottle has been filled a small quantity of blood is run through the tube of the taking set into this pilot tube, which is already in place in the stopper. Finally, the aluminium cap with its rubber disk is screwed firmly down to seal off the pilot tube. The accompanying diagram shows the stopper and tube in place and the cap closed. With this method the bottle and the tube are independently sealed, and there is no possibility of the pilot tube becoming separated from its parent bottle.—I am, etc.,

Northampton. E. A. J. ALMENT.

Treatment of Threadworms

SIR,—Patients with hookworm disease often have an intense and persistent craving that compels them to eat earth and mud. Is it possible that the ancylostoma, in order to satisfy its own needs, influences the host in some subtle manner to supply the soil or mineral that it requires?

Children who harbour threadworms are reputedly always hungry, especially for sweets and sugar, and this is commonly taken by mothers and the laity as a diagnostic sign of the disease. Is this another example of a similar effect by a worm? This was the theory, admittedly erroneous, that suggested it may be possible to eradicate threadworms by altering the diet in such a way as to deny them the food they desired and "starve them out." It

was noticed that the patients who suffered from threadworms were either children or pregnant women in both of whom the diet was a low-protein high-carbohydrate one as compared with that of the general population. These patients were therefore treated by altering the diet so as to decrease the carbohydrate and starch and increase the protein and fat. Sugar was eliminated as far as possible, starchy foods were reduced, and meat, fish, eggs, and butter were given in increased amounts. For example, the usual breakfast of cereal and sugar, bread and jam, was replaced by one of bacon and egg with bread fried in fat. The amount of milk was not changed. A mild laxative was used once or twice a week but was later given up as unnecessary. The results were consistently and entirely satisfactory, complete cure being achieved in about two weeks, and relapses did not occur while the patient was on this adult type of diet. During twenty years of busy general practice I treated a great number of patients with threadworms by this method with unvarying success, and I am convinced that dietary measures are simpler, more efficacious, and preferable to treatment by vermifuges and enemata.

Confirmatory evidence of the link btween diet and threadworms will be provided by older obstetricians, who will remember the prevalence of this infection in those pregnant women who avoided protein because of its supposed injurious effect on their kidneys compared with its absence since the modern high-protein low-carbohydrate diet has been adopted. Some explanation is required to account for threadworms being predominantly a disease of childhood, for surely everyone is equally liable to infection. From my experience it would seem that the presence and persistence of threadworms in a patient depend on the chemistry of the bowel contents which makes the environment favourable for their growth, and that this is to a great extent dependent on the diet.

I should be interested to learn if threadworm infection is more prevalent in Great Britain since the reduction in the consumption of meat, or has this been replaced by adequate protein from other sources?—I am, etc.,

Melbourne, Australia. IVON HAYES.

The British X-ray and Radium Protection Committee Valedictory

SIR,—A disturbing series of deaths amongst early workers with *x* rays led a small group of their surviving colleagues in 1921 to formulate some rules which would prevent a continuance of such casualties. Thus was born the British *X*-ray and Radium Protection Committee. The late Sir Humphry Rolleston consented to become its first chairman. Under him, and largely financed by him, the first memorandum was issued in July of that year and the first detailed report followed in 1923. The code was welcomed by all classes of radiological workers and formed the basis for similar recommendations in most countries of the world and for subsequent international recommendations.

Towards the end of the war the Medical Research Council set up a Committee on the Medical and Biological Applications of Nuclear Physics. Its subcommittees, and particularly the Tolerance Doses Panel, under the chairmanship of Professor Mayneord, produced a large series of papers dealing with the fundamental data upon which protection measures for all those dealing with sources of ionizing radiations could be formulated. With the passing of the Radioactive Substances Act, a statutory committee came into existence. Whilst the Medical Research Council groups are concerned with the research aspects, the statutory committee has a duty in respect of regulations and licences, and is concerned with codes of practice over the whole extensive field now to be covered. In these circumstances the British *X*-ray and Radium Protection Committee, which, despite its lack of any statutory authority, had attained international status, had lost its *raison d'être*. A final meeting was held in September, 1952.

The passing of a committee through which Great Britain set a pattern for the world would seem to be a landmark that deserves record. At the suggestion of its last chairman, this letter is signed by the two surviving members of the 1921 meeting.—We are, etc.,

London. CUTHBERT ANDREWS.
SIDNEY RUSS.

Obituary

HAROLD BALME, O.B.E., M.D., F.R.C.S.

Dr. Harold Balme, who died in London on February 13 at the age of 74, contrived, with conspicuous success, to live a life full of interest to himself and of great benefit to his fellow men. Towards the end of his professional life he became a leading authority on rehabilitation.

Harold Balme was born in London on May 28, 1878, the son of Mr. Paul Balme, and received his medical education at King's College and King's College Hospital. He won the Worsley scholarship in 1898, and in the course of his studies he won the Warneford, Leathes, and Todd prizes in medicine. As his aim was to become a medical missionary, he also studied divinity and won the Barry Prize. The outbreak of war in South Africa in 1899, however, upset his plans temporarily, for, like many others of his generation, he responded to the call for volunteers, and from 1900 he served with the Imperial Yeomanry Field Hospital, being awarded the war medal with three clasps. After the war he returned to London, and qualified by taking the M.R.C.S., L.R.C.P. in 1903. He then held the posts of resident medical officer at the London Medical Mission and clinical assistant at the Royal Eye Hospital and at King's College Hospital, and in 1905 he obtained the F.R.C.S. In the following year he went to China as a medical missionary at Taiyuanfu, in the Shansi province. In 1913 he was appointed professor of surgery in Cheeloo University (formerly known as the Shantung Christian University) at Tsinan and superintendent of the University Hospital, later becoming dean of the medical school. He became president of the University in 1921 and chairman of the first Council on Medical Education in China and president of the Council on Higher Education. His services to the profession in China were recognized by his election as an honorary member of the National Medical Association of China. He was elected also an Associate of King's College. A record of his experiences and his work is to be found in his book, *China and Modern Medicine: A Study in Medical Missionary Development*. Dr. Balme relinquished his appointment as president of the Cheeloo University in 1927 and returned to England to engage in consultant practice. In the following year he graduated M.D. at Durham University.

During the last war he worked in the Emergency Medical Service and became medical superintendent first of the Haymeads Hospital at Bishop's Stortford and later at Pinderfields Hospital, Wakefield. Before the war there was very little in the way of an organized service to help the disabled return to work, and of course as the war went on the need for such a scheme grew greater. Balme became one of the first to work in this field, and his services were recognized by his appointment as O.B.E. in 1942. Later on during the war he became the Ministry of Health's adviser on rehabilitation, and he brought to that task the same enthusiasm and energy he displayed in everything else he undertook. In 1944 he wrote a booklet for the British Council entitled *The Unfit Made Fit*. After the war he became consultant adviser on rehabilitation to the United Nations, the World Health Organization, and the United Nations International Children's Emergency Fund, work which took him to many European countries. Last September he was in Sweden directing the group training course

on the rehabilitation of the adult disabled, and in the previous May he was present at the opening by the President of the Austrian Republic of the rehabilitation and training centre at Tobelbad, near Graz, a centre which Dr. Balme himself described in an article published in this *Journal* on November 15, 1952.

During his work in China Dr. Balme published many articles on a variety of medical subjects, including one with the intriguing title, "Intussusception Through the Neck of an Opium Lamp-glass Shade" (*China Medical Missionary Journal*, 1907). After his return to London he wrote a book on *The Relief of Pain* (1936), and another entitled *A Criticism of Nursing Education, with Suggestions for Constructive Reform*. In the writing of this book his experience as a member of the council of the Royal College of Nursing stood him in good stead.

Dr. Balme married Miss Hilda E. Carr, of Carlisle, in 1910, and she survives him, together with their only son, who is principal of the University College of the Gold Coast.

Dr. C. F. HADFIELD writes: Dr. Harold Balme's great administrative ability was put to a severe test when in 1939 he was appointed medical superintendent of the Haymeads E.M.S. Hospital at Bishop's Stortford. An initial difficulty was that this was an office which had never previously existed, and still apparently did not exist. Haymeads was an infirmary rather than a hospital and so had no medical superintendent, its medical needs being served from outside by a local practitioner. All real control was in the hands of the local and county council authorities. The buildings were old and inconvenient, there being only two wards in any way approaching modern standards. There was not even a dispensary of any kind. From such beginnings Dr. Balme succeeded in threading his way through a network of local customs and established routine, and so laying the foundations of what quickly developed into a really well-equipped and modern hospital of some 800 beds. One secret of his success was the manner in which he speedily obtained the loyal support of his medical staff. This staff had been collected from a variety of sources, and at the start most of its members were quite unknown personally to himself or to each other. By means of friendly contacts, and almost daily staff consultations, he quickly converted it into a homogeneous, friendly, co-operative, and, it may be claimed, efficient unit.

Professor JOHN KIRK writes: To remember Harold Balme is like contemplating a giant tree in the forest, a monarch supreme, and pre-eminent among its kind. Those of us who were privileged to know him in his China days will always count that experience as one of the gladdening and enriching episodes of our lives; here was a man endowed with intellectual gifts of the highest order, possessing outstanding medical skill, and having powers of administration and leadership which marked him out in any company. Yet, when one has recognized and said all that, one feels that one has completely failed to describe the true greatness of Harold Balme. As one seeks to account for the impression he made on his colleagues and friends, one realizes that springing up in him and overflowing from him was an exuberance of spiritual freshness and buoyancy which pervaded all his life and made even an occasional meeting with him a tonic of happiness. It was in China that I knew him best, and there the effect of his life upon his Chinese colleagues and students was just as sure and noticeable as upon those of his own race. One of my early impressions was of discovering his fluency in the Chinese language and his ability to give lectures on surgery in the Shantung medical school which were not only completely intelligible but eagerly appreciated by his students. As a medical missionary in planning and in action he was alike superb. He was not only a skilled clinician, but his compassion flowed continuously from his heart to his fingertips. He was an eloquent and convincing speaker and a gifted writer. With statesmanlike vision he grasped the truth that for the West to extend the benefits of modern medical science to China without at the same time giving her a medical profession enlightened and inspired by the Christian faith was to discharge only half of the obligation. Thus medical education in an atmosphere like that of the Shantung Christian University won and held the utmost loyalty and energy of his mind and heart. The world does not often see men like Harold Balme, and though our sense of sorrow at his passing is inevitable our deep sense of thankfulness for his life overwhelms the sorrow.

RANSOM PICKARD, C.B., C.M.G., M.D., M.S. F.R.C.S.

We record with regret the death of Colonel Ransom Pickard, the well-known ophthalmic surgeon, at his home at Exeter on February 9 at the age of 85.

Ransom Pickard, who was born on May 18, 1867, received his medical education at St. Bartholomew's Hospital, qualifying in 1889 and graduating M.B. in the same year. He won the gold medal in medicine and gained first-class honours in forensic medicine and honours in obstetrics. After qualifying, he held appointments as ophthalmic house-surgeon at St. Bartholomew's Hospital and clinical assistant at Moorfields Hospital. Between 1891 and 1893 he obtained the B.S. with first-class honours, the F.R.C.S., the M.D., and the Cambridge D.P.H. Having acquired all these distinctions, Pickard elected to live at Exeter, where after a few years in general practice he established himself as a consultant ophthalmologist, being elected to the staff of the West of England Eye Infirmary. He acquired a great reputation, both locally and nationally, as an ophthalmic surgeon, and from 1934 to 1936 he was president of the Section of Ophthalmology of the Royal Society of Medicine. One of his special interests was glaucoma, and he published several papers on this and other eye diseases. His hospital work was all-important to him, but it was inevitable that one who took such pains with his patients should build up a large consulting practice, and his reputation spread far and wide. His character and ability soon brought him into prominence in civic affairs, and he was sheriff of Exeter in 1906–7 and mayor in 1926–7. He took a great interest in the University College of the South-west, of which he became a vice-president.

In the first world war he served in the R.A.M.C., and was placed in command of the 1st Wessex Field Ambulance, which he had helped to raise. He went to France immediately war broke out, and later was promoted to colonel and appointed A.D.M.S. of the 48th Division, with which he served in Northern Italy. He was five times mentioned in dispatches, and for his services he was appointed C.M.G. in 1916 and C.B.E. in 1919. He also received the Italian Croce della Guerra. During the last war he served as chairman of the local medical war committee.

A member of the British Medical Association for 58 years, Pickard served as one of the honorary secretaries of the Section of Ophthalmology when the Association held its Annual Meeting at Exeter in 1907, and he was a vice-president of the same Section at Portsmouth in 1923. He was president of the South-western Branch of the Association in 1927–8, and was also on the Ophthalmic Committee for some years.

Pickard developed a great love for the West of England, and for Devon in particular. At one time he was a keen mountaineer, but as the years went by he took his exercise in the form of long country walks,

on which his wife usually accompanied him. He was a past president of the Devon Archaeological Exploration Society, and in 1947 he published a monograph on *The Population and Epidemics of Exeter in Pre-Census Times.* A lifelong Methodist, he was a non-smoker and teetotaller, but was never one to thrust his personal views upon others. In 1912 he married Miss Mabel Lucy Childe, and the sympathy of all his many friends will go to his widow. By Colonel Ransom Pickard's death Exeter has lost a fine citizen and the medical profession a worthy and distinguished member.

Sir HOLBURT WARING, Bt., C.B.E., M.S., F.R.C.S.

We are indebted to Mr. R. W. RAVEN for the following appreciation:

The death of Sir Holburt Waring, whose obituary notice was published in last week's *Journal* (p. 456), diminishes further the number of those outstanding men who played such an important part in guiding and developing British surgery during the first half of this century. Each in his particular way made an important contribution. Few have possessed like him such ability in so many fields, or the clear vision which penetrates so far into the future and the deep convictions providing the motive force for action. He was a dominant figure for many years, and time was granted him after retirement to see many of the results of his labours. As one of those privileged to receive his early surgical training from Sir Holburt, may I offer my tribute to his memory? His old house-surgeons cannot fail to look back with gratitude upon the time we worked for him, when the fundamental principles of surgery were instilled into us and our habits of thought and reactions were consolidated. He set a high standard without leniency and his methods were a ritual. How much we admired his wonderful hands as we watched him examine a patient or assisted him at operations. What a depth of surgical knowledge and experience there was to draw from. In his home we also probed beneath the surface and found a deeper feeling and a friend. He was always greatly interested in the problems of cancer, and his book *The Surgical Treatment of Malignant Disease* is full of his mature surgical wisdom.

Sir WILLIAM DOUGLAS, G.C.B., K.B.E.

The many friends of Sir William Douglas, Permanent Secretary to the Ministry of Health from 1945 to 1951, will have heard with great regret of his death on February 17. He was 62 years of age. We are indebted to Sir WILSON JAMESON for the following appreciation:

When Sir John Maude retired from the office of Permanent Secretary to the Ministry of Health in 1945, most of the preparatory work for the proposed National Health Service had been done. A Bill had been drafted and might well have been presented to Parliament had not the war in Europe come to an end and a Labour Government taken the place of the wartime Coalition. Who was to be the new Parliamentary Secretary? The appointment was nearly as important as that of the new Minister. The choice fell upon Sir William Douglas (Willie Douglas to all his Civil Service contemporaries), and he rather unwillingly left the Ministry of Supply for what he knew would be something of a political storm centre for the next few years. Douglas was a born negotiator. He was attractive in appearance and persuasive in speech. He was in his element as chairman of a conference. No matter how awkward the question put to him or how unpleasant the decision he had to impart, he would give his tie a twist and his head a shake, and the situation would be dealt with in such a way as to cause the least possible ill-feeling. Though he was at times sorely tried by the protracted arguments and discussions with the various sections of the medical profession prior to the appointed day, he always retained his good humour and his debonair manner. He was a good friend to the doctors, as members of the B.M.A. know very well. I myself could not have wished for a kinder or more helpful colleague. Unlike his predecessor, he rarely put pen to paper. His business was to see people and to talk to them, not to draft letters or memoranda. All his drafting was done for him, and he was fortunate in having such able assistants.

As one would expect, Douglas had lots of friends. He was a good golfer, and no Civil Service golf meeting was complete without him. It was strange, too, how often official business took him north when an international was staged at Murrayfield. He had made all his plans for a happy and useful retirement and had just got well into his stride when his fatal illness overtook him. The Ministry of Health and the medical profession were fortunate in having his help during those critical five years.

Dr. A. ESMEE RUCK was brutally murdered at her home in Kenya on the night of January 24, together with her husband, Mr. Roger Ruck, and their only child, Michael, aged 6 years. Adeline Esmee Ruck, better known to her colleagues by her maiden name of Esmee de Smidt, was born at Cambridge in July, 1920, the only child of Captain F. P. G. de Smidt, a member of the medical profession who had a distinguished career as a bacteriologist, and who served in the Colonial Medical Service in Kenya from 1926 to 1936, when ill-health caused his retirement. Esmee de Smidt was educated at the Limuru Girls' School and at the Kenya High School, and graduated M.B., Ch.B. from the University of Capetown in 1943, thus becoming the first woman pupil of a school in Kenya to graduate in medicine. In 1945 she was appointed a temporary medical officer in Kenya, serving in the Native Civil Hospital, Nairobi, and working chiefly among the children of the Kikuyu tribe. The children, for whom she had a real affection, made up the majority of the patients in the overcrowded ward in which she laboured. A year later she had to give up the work when she became herself a mother. In 1947 she took the D.P.H. at Capetown and returned to Kenya, where in recent years she had conducted a dispensary for Africans in the farming area in which she and her husband had settled. Dr. Ruck had a winning way which tended superficially to cloak her fine intellect. Though never robust in health, she accepted the reverses of life with fortitude and devoted herself to her profession, to her husband, and to their only child. While fully conscious of the danger which surrounded her home, she felt it her duty to remain there and was looking forward to restarting the dispensary for Africans in a few months' time, when her son was due to leave for a boarding-school. That the three should be deliberately and savagely killed in one night is a tragedy indeed for Kenya. Dr. Ruck is mourned by her professional colleagues of all races. She is survived by her invalid widowed mother, to whom our deepest sympathy is extended. —F. J. W.

With the death of Dr. W. W. HORTON on February 4, within a few days of his 95th birthday, one of the few remaining links with the Edinburgh of the 'seventies has been severed. Born on February 10, 1858, Wilfred Winnall Horton was educated at Shrewsbury and at the University of Edinburgh, which he entered in 1875. He graduated M.B., C.M. in 1880, and proceeded M.D. four years later. After holding appointments at a number of mental hospitals, Dr. Horton was in general practice, first in the U.S.A. and then for 20 years at Malvern. In 1915 he entered the R.A.M.C. and was attached to the Gloucestershire Regiment. On being invalided out of the service in 1917 he became medical superintendent of Wye House, a private mental hospital at Buxton, and remained there for 22 years, retiring at the age of 81. On the rare occasions he talked about his early days, Dr. Horton would describe his student years as being a time of transition, especially in surgery.

His reminiscences were full of interest. He had seen operations performed in a carbolic spray produced by a steam kettle; he knew Cunningham as an able demonstrator in anatomy and Huxley as a temporary lecturer—"interesting, but far above the heads of the students most of the time." He remembered James Spence operating in an old frock-coat kept for the purpose and scorning Lister's newfangled antiseptic methods; Lister himself, lecturer in clinical surgery, a revered figure; and finally Joseph Bell, extramural lecturer in surgery, who entertained the students by displaying his remarkable powers of observation and was afterwards immortalized by Conan Doyle in the person of Sherlock Holmes. Dr. Horton was much loved by his patients, both in general practice and in mental hospital work, and he stood for all that is best in the profession to which he belonged for over 70 years.

Dr. E. A. BARTON, a well-known general practitioner in Kensington before his retirement, died at University College Hospital on February 10 at the age of 89. Born on July 12, 1863, the son of the late Dr. A. B. Barton and a nephew of Mr. Berkeley Hill, a surgeon at University College Hospital, Edwin Alfred Barton, who was educated at Harrow, was originally intended for the Army, but he decided to follow in his father's footsteps and studied medicine at University College Hospital, where he qualified in 1887. While holding an appointment as house-physician he had under him as clerks such men as Leonard Hill, George Murray, of Newcastle-upon-Tyne, who became notable for his work on the thyroid, and Herbert Tilley, later well known as a throat specialist. Subsequently he obtained the coveted post of outdoor obstetric assistant. In his book *A Doctor Remembers* he described the dirt, squalor, and drunkenness which were then rife in the districts around University College Hospital. After further hospital work he went into partnership with an elderly doctor in Kensington Square in 1890, and remained in practice in Kensington for 40 years, retiring in 1930. On the outbreak of war in 1914 he offered his services to University College Hospital, where he became anaesthetist to out-patients. Later he became medical officer to the hospital's child welfare department. Dr. Barton had many outside interests, being a keen photographer and fisherman, and a vice-president of the Flyfishers' Club. In addition to the book mentioned above, he wrote *Essentials of Infant Feeding* (1925), *Chalk Streams and Water Meadows* (1933), *Running Water* (1944), and *An Album of the Chalk Streams* (1946). Some years ago he contributed a sincere and impressive article entitled "Death and Euthanasia" to the *University College Hospital Magazine*. He married Margaret E. Pittis in 1895, and she, with their daughter, survives him.

Medical Notes in Parliament

Medical Research in Scotland

The Hospital Endowments (Scotland) Bill was given a second reading in the House of Lords on February 18.

The EARL OF SELKIRK explained that it was based on the recommendations of the Hospital Endowments Commission, which was established to prepare schemes for the regulation of endowments transferred to hospital boards of management under the National Health Service (Scotland) Act. The Commission had recommended that part of these funds should be devoted to research, under an independent trust, and it was estimated that about £120,000 a year would be available for the purpose. There was a wide measure of support for the scheme in Scotland. The Chairman of the Commission, Sir Sydney Smith, had borne in mind that adequate funds must be available to provide reasonable amenities at individual hospitals, and had said that even when a research fund had been provided the hospitals would be reasonably catered for.

The Bill set up the trust, and empowered the Endowment Commissioners to transfer funds to it. The Chairman and members of the trust would be appointed by the Secretary of State, and would probably number about seven. The trust would be able to receive also legacies and gifts. They were to consult an advisory committee, which in the first instance would be the Advisory Committee on Medical Research under the chairmanship of Sir Edward Appleton, Principal of Edinburgh University. This body had links with the Medical Research Council, so that as far as possible there would be no overlapping or difficulty, and information would be circulated as widely as possible.

LORD INMAN attached particular importance to money given for definite purposes being used for those purposes if at all possible, and to the importance of consultation with other research bodies to avoid overlapping.

LORD KINNAIRD asked if the trustees would be able to consider applications for grants for research work in hospitals outside the National Health scheme, and instanced the research work on tuberculosis at two hospitals near Aberdeen run by the Scottish branch of the British Red Cross.

The EARL OF SELKIRK said that it was implicit in the Bill that funds given for specific purposes should not be diverted to uses antagonistic to the donors' intentions. It was clear from the report of the Endowments Commission that there would be adequate funds available for the hospital management boards. The total capital of the funds was about £13m. The purpose of the Bill was to enable the trustees to assist any medical purpose that might be brought to their attention if they thought it worthy of assistance. It mattered not whether the establishment concerned was connected with the National Health Service or was a private hospital, a university, or any other organization, if they considered it most useful to promote a particular type of research.

Proprietary Medicines

Mrs. JEAN MANN asked on February 17 about the amount spent in prescriptions in 1950, 1951, and 1952 on slimming tablets, and what researches the Scottish Office had made to satisfy itself as to the value of these tablets in reducing obesity.

Commander T. D. GALBRAITH replied that detailed information was not available. He had no reason to think that doctors were prescribing drugs which were not of value, when taken under medical supervision, in cases where weight reduction was necessary on medical grounds.

Mrs. MANN referred to a report that £400,000 had been spent on slimming tablets, and asked the Minister to confirm whether the tablets really slimmed or merely curbed the appetite.

Commander GALBRAITH replied that "dexedrine," to which Mrs. Mann referred, was quite an effective drug for slimming when used under medical supervision, and slimming was not the only purpose for which it was prescribed.

Mrs. MANN also asked on February 17 what number of patients had transferred from doctors who refused to prescribe advertised proprietary drugs to others who would do so, and if the Secretary of State would protect doctors from this form of pressure.

Commander GALBRAITH told her that no statistics were available. Various forms of publicity had emphasized that it was for the doctor, not the patient, to decide what was to be prescribed, and he looked to the doctors to support one another in this matter.

Dr. EDITH SUMMERSKILL and Mr. A. BLENKINSOP questioned the Minister of Health on February 19 about the prescribing of proprietary medicines, Dr. Summerskill asking whether the Minister's attention had been drawn to the report of the Comptroller and Auditor-General with regard to the heavy prescribing of expensive proprietary drugs, and what action he proposed to take in order to reduce this expenditure in future.

Mr. IAIN MACLEOD replied that all doctors had been urged to help to keep this cost down by prescribing standard drugs wherever appropriate and by not prescribing proprietary drugs which were advertised direct to the public. In the last resort it was in the power of the doctors themselves to help most in this considerable problem, and he was sure that he could count on them to do so. He was considering what further steps could be taken.

Civil Service M.O.s

Dr. A. D. D. BROUGHTON asked the Chancellor of the Exchequer why he had not raised the salaries of Civil Service medical officers to conform with the increase in remuneration granted to general medical practitioners under the Danckwerts award. Mr. J. A. BOYD-CARPENTER, the Financial Secretary, who replied, referred him to Mr. Butler's statement last July, to the effect that Mr. Justice Danckwerts's award was confined solely to the remuneration of general practitioners in the National Health Service and had no wider application.

Dr. BROUGHTON pointed out that these medical officers, who performed their responsible duties very efficiently, had been affected like everyone else by the rise in the cost of living. Would the Treasury reconsider the question of revising their salary scales to bring them into line with their professional colleagues in other branches of medicine?

Mr. BOYD-CARPENTER said the salaries of Government servants were kept under constant review. The present scale of salaries of these officers was that recommended by the Howett Committee, which reported as recently as August, 1951.

Toxic Sprays

Sir RALPH GLYN asked the Minister of Agriculture on February 19 whether he would consider issuing immediate circulars to the county agricultural committees advising that no spraying of weeds or any crops with dinitro*ortho*cresol should be carried out without reference to the committees; and whether he would amend the Agriculture (Poisonous Substances) Act to necessitate obtaining a licence before poisonous sprays could be used on land, in view of the damage that was being done to insects, birds, and animals as the result of the application of these chemical substances to large tracts of agricultural land; and whether he would set up a committee, not altogether composed of chemists, to report on the results, during 1952, of the spraying of poisons to destroy noxious weeds.

Sir THOMAS DUGDALE replied that he had no power to require prior notification of spraying, but he was keeping a careful watch on developments. The long-term solution to the problem was the production of equally effective sprays that were not toxic to wild life. Research into this and other aspects was continuing under the supervision of the Agricultural Research Council. He was asking Professor Zuckerman and his Working Party on Precautionary Measures against Toxic Chemicals used in Agriculture to consider the general question of effects on wild life, when they had completed their present study of possible risks to the consumer.

After the Floods

Mr. T. C. PANNELL commented in the debate on the floods on February 19 on Ministry of Health administration. Many people, he said, had lost spectacles, dentures, and surgical appliances, but there seemed to be no clear knowledge whether there would be free replacement. There was also the question of prescription charges.

Mr. HAROLD MACMILLAN, Minister of Housing and Local Government, referring to this in his reply, said that during the emergency period the Minister of Health had used the Nelson technique and turned a blind eye to the giving of prescriptions without charge, and the supplying of artificial teeth or spectacles, perhaps without authority. It would be wise to leave the matter there.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 7** (No. 5) and corresponding week 1952.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	16	0	12	0		24	2	14	0	0
Dysentery	286	29	117			490	56	78	3	
Encephalitis, acute	4	0	1	0		5	0	0	0	
Enteric fever:										
Typhoid	2	1	0	0	2	5	0	1	1	1
Paratyphoid	15	0	0	0	0	6	0	0	0	
Food-poisoning	76	11		0		94	6		0	
Infective enteritis or diarrhoea under 2 years				11	29				7	29
Measles*	31,494	1661	292	92	294	3,386	50	319	160	43
Meningococcal infection	45	2	14	1	4	31	1	17	2	2
Ophthalmia neonatorum	42	4	5	0		30	2	9	0	1
Pneumonia†	2,338	199	253	34	9	1,005	55	308	11	1
Poliomyelitis, acute:										
Paralytic	20	3	1	0	2	17	3	1	1	2
Non-paralytic	6	0				8	1			
Puerperal fever§	260	31	13	1		257	46	8	1	2
Scarlet fever	1,545	58	270	43	52	1,320	109	241	16	31
Tuberculosis:										
Respiratory			158	31				157	35	
Non-respiratory			30	1				25	4	
Whooping-cough	2,571	131	204	44	134	2,652	83	345	120	53

DEATHS in Great Towns	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	1	0		0	0
Dysentery	0	0		0		2	1		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0		0	
Infective enteritis or diarrhoea under 2 years	10	0	0	0	1	18		1	0	2
Influenza	446	89	2	2	2	47	9		3	0
Measles		0	0	0	0		0		0	0
Meningococcal infection		0	0				0			
Pneumonia	667	138	21	20	9	341	59		18	9
Poliomyelitis, acute	3	0			1	4	0			0
Scarlet fever		0	0	0	0		0		0	0
Tuberculosis:										
Respiratory	150	27	15	1	8	170	20	21	4	6
Non-respiratory		5	7	0	4		1	0	1	3
Whooping-cough	3	0	0	0	1	4	0		0	0
Deaths 0–1 year	291	42	33	10	9	275	25	38	10	17
Deaths (excluding stillbirths)	8,252	1545	601	142	177	6,938	1008	837	168	216
LIVE BIRTHS	7,155	1037	876	202	389	7,457	1117	857	208	329
STILLBIRTHS	179	28	19			185	22	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Births and Marriages in 1951

In England and Wales there were 677,529 live births in 1951, giving a birth rate of 15.4 per 1,000 population.[1] This was a decrease of 0.4 from the rate for 1950, when there were 697,097 live births. The average rate for the years 1936–40 was 14.7 per 1,000. There were 32,771 illegitimate live births, comprising 4.8% of the total number of live births. Stillbirths numbered 15,985; this gave a rate of 23 per 1,000 total live and stillbirths—the same as for the previous three years.

There were 360,624 marriages. This figure gives a rate of 16.4 persons married per 1,000 population. A feature of these marriages was their peak in March. Over 21% of the year's marriages were celebrated in that month. The nearest approach to this was in 1950, also in March, when the figure was 14%. These peaks of incidence are much influenced by the date of Easter and of the end of the income-tax year.

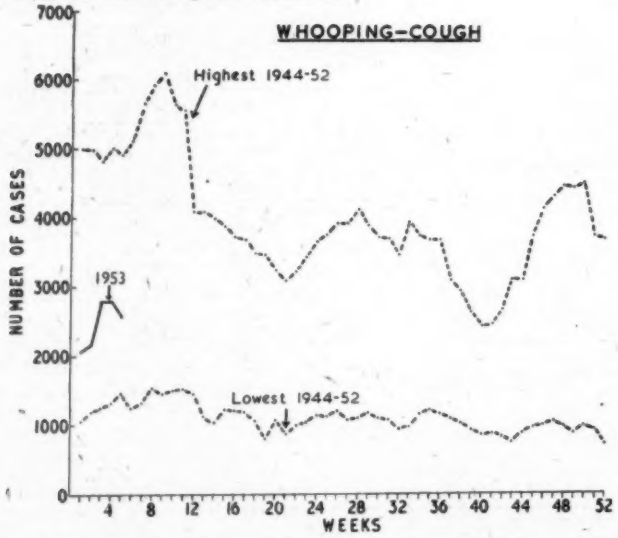
The number of new petitions for divorce rose from 29,729 in 1950 to 38,382 in 1951. (The facilities provided by the Legal Aid and Advice Act, 1949, became available from October 2, 1950.) The number of dissolutions and annulments of marriage made absolute was 28,767. Of these, 2,970 related to marriages of less than five years' duration, 9,063 to marriages of 5 to 10 years' duration, 7,011 to marriages of 10 to 15 years' duration, 4,047 to marriages of 15 to 20 years' duration, and 5,676 to marriages of 20 years and over. In 9,895 cases there were no children of the marriage, in 9,678 cases there was one child, and in 5,197 cases there were two children.

50,339 confinements took place within eight and a half months of marriage, and of these 35,997 occurred within six and a half months of marriage.

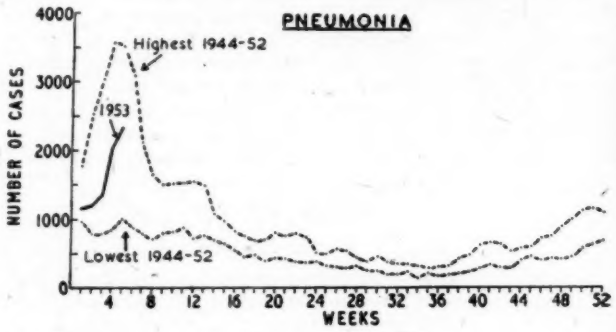
Under the Legitimacy Act, 1926, 2,596 births originally registered as illegitimate were re-registered as legitimate on the subsequent marriage of the parents. This is the lowest number in any year since the operation of the Act.

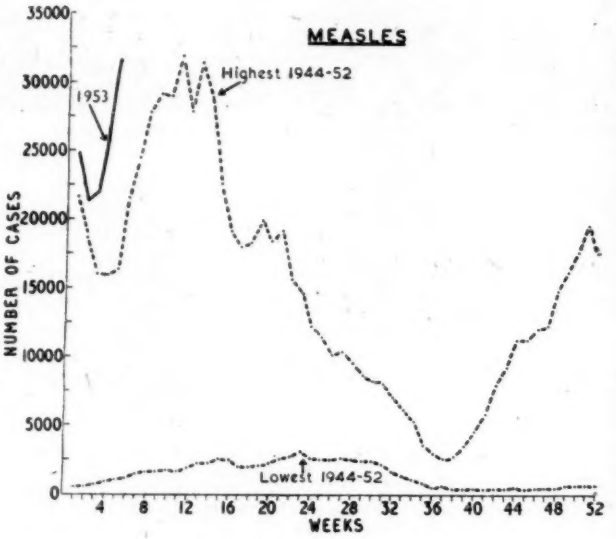
Graphs of Infectious Diseases

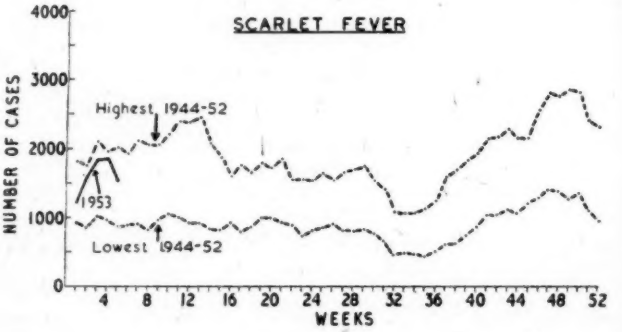
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - - -, the figures for 1953 thus ————. Except for the curves showing notifications in 1953, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



[1] *Registrar-General's Statistical Review, 1951*, Tables, Part II, Civil. H.M.S.O. 5s.







Infectious Diseases

In England and Wales during the week ending February 7 notifications of measles increased by 5,034, from 26,460 to 31,494, and acute pneumonia by 309, from 2,029 to 2,338; while decreases of 305 were recorded for scarlet fever, from 1,850 to 1,545; 228 for whooping-cough, from 2,799 to 2,571; and 149 for dysentery, from 435 to 286.

The largest rises in measles notifications during the week were 577 in Surrey, from 908 to 1,485; 358 in Kent, from 1,082 to 1,440; 313 in Derbyshire, from 733 to 1,046; and 235 in Hertfordshire, from 640 to 875. The largest decrease in the incidence of scarlet fever was 44 in Yorkshire West Riding, from 185 to 141. The largest fluctuations in the trends of whooping-cough were a rise of 39 in Yorkshire West Riding, from 239 to 278, and a fall of 48 in Wiltshire, from 63 to 15. 16 cases of diphtheria were notified, 8 fewer than in the preceding week; 4 cases were notified in Wales compared with none in the previous week.

15 cases of paratyphoid fever, 8 more than in the preceding week, were notified. The rise was mainly contributed by Wales, where 11 cases, 10 more than in the previous week, were notified. The chief centre of infection was Caernarvonshire, Bangor M.B., 6.

26 cases of acute poliomyelitis were notified during the week; these were 2 fewer for paralytic and 1 fewer for non-paralytic cases than in the preceding week. The largest returns were Somersetshire 4 and London 3.

The largest returns for dysentery were Lancashire 65 (Liverpool C.B. 19, Oldham C.B. 10); Lincolnshire 37 (Grimsby C.B. 30); London 29 (Chelsea 6); Yorkshire West Riding 24 (Barnsley C.B. 15); Essex 22 (East Ham C.B. 19); and Middlesex 19 (Edmonton M.B. 13).

The deaths from influenza in the great towns numbered 446, being 133 more than in the previous week. 61% of the deaths were registered in London and the south-east region.

Influenza

There were 530 deaths from influenza in the great towns of England and Wales in the week ending February 14. This is an increase of 84 over the previous week's total of 446. The northern half of the country experienced a greater increase than the southern, though the majority of the deaths (274) occurred in London and the south-east. First claims on the Ministry of National Insurance were falling in London and the south, but showed a moderate rise in the north. Since the beginning of the year there have been 1,544 deaths from influenza in the great towns compared with 237 in 1952 and an estimated 6,460 in 1951.

Week Ending February 14

The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,515, whooping-cough 2,238, diphtheria 24, measles 32,359, acute poliomyelitis 17, dysentery 320, paratyphoid fever 6, and typhoid fever 4.

The measles notifications constitute the highest weekly total to be recorded since notification was made compulsory in England and Wales in 1940.

Medical News

N.H.S. Estimates.—The cost of the Health Service in Britain for the next financial year (1953–4) is estimated at £416,480,360. This is a reduction of over £22m. on the estimates for the current year.

Royal College of Surgeons in Ireland.—The time-honoured Charter Day Dinner of the Royal College of Surgeons in Ireland was held on February 14 in the Large Hall of the College. Some 180 Fellows and their guests attended. Before the dinner Sir Gordon Gordon-Taylor was admitted to the Honorary Fellowship of the College by the President, Mr. Michael Burke. In presenting Sir Gordon for admission Mr. William Doolin, the Secretary of the Council, described his name as already "almost a legend, intimately associated with certain of the less frequent, more daring, not to say heroic, procedures in modern surgery." They welcomed him, too, as a Scotsman, for that "subtle blend of Celtic qualities which so often puzzle the Sassenach—the high courage and temper of the Highlander and the sentimental humour of the Lowlander." At the dinner, the toast of "Our Guests" was proposed by Mr. Ian Fraser, Vice-President, and was replied to by Sir Gordon in a characteristically graceful speech. The toast of "The College" was proposed by Dr. Edward Freeman, P.R.C.P.I., and was responded to by the President, Mr. Burke.

Surgeons' Hall of Fame.—The International College of Surgeons is planning a Surgeons' Hall of Fame at its Chicago headquarters to commemorate illustrious surgeons and their work. A large mansion has been acquired for the purpose, and a board of 12 trustees, of whom Sir Zachary Cope is one, has been appointed. An electoral college, composed of representatives from all over the world, will decide which surgeons are to be honoured in the Hall. The International College of Surgeons has about 10,000 members, drawn from 71 nations; about half its membership is from the United States. The College was founded in 1935 by Dr. Max Thorek in Geneva, and in 1940 moved to America.

Local Medical Societies.—Recent meetings have included the following: *Manchester Medical Society.*—On January 13 three short papers were read to the Section of Surgery on "Continuous Scoline for Relaxation in Abdominal Surgery" (Dr. M. Swerdlow), "The Effects of *X*-ray Contrast Media in the Arterial Circulation" (Mr. R. P. Jepson), and "Pneumomediastinum following Block Dissection of the Neck" (Mr. H. F. Smith). On January 14 Professor L. J. Witts read a paper on "Ulcerative Colitis" to the Sections of Medicine and Pathology. During it he referred to an M.R.C. therapeutic trial of cortisone, which it was hoped would eventually settle whether cortisone was indicated in that disease. Hospitals from five regions were co-operating in the trial. *Devon and Exeter Medico-Chirurgical Society.*—On January 15 Mr. C. C. Jeffery gave an address on "The Closed Treatment of Fractures of the Forearm." On February 5 Dr. C. J. Fuller read a paper drawing attention to a small group of cases in which dysphagia is associated with lung complications. There was always an oesophageal anomaly of some kind, and pulmonary infection occurred by spilling over of oesophageal contents. *Liverpool Medical Institution.*—On January 22 a pathological meeting was held. Dr. A. H. Cruickshank described a case of Chiari's disease; Dr. K. McCarthy read a short paper on "Generalized Vaccinia," in which he described a rare and fatal case in a child who had no globulin in her serum, failed to develop neutralizing antibodies, and had a persistent viraemia up to her death seven weeks after vaccination; Dr. M. K. Alexander described a fatal case of the Stevens–Johnson syndrome with fibrinoid necrosis of the arterioles in the stomach, liver, and spleen. On February 12 Mr. Ronald Edwards gave an address on "The Present Position of the Surgery of the Heart and Great Vessels." *Chelsea Clinical Society.*—On February 10 there was a discussion on the importance of leisure, opened by Mr. John Betjeman, and continued by Sir Heneage Ogilvie and Mr. Gilbert Harding. *North of England Obstetrical and Gynaecological Society.*—On February 20 there was a joint discussion in Liverpool with the *North-western Tuberculosis Society* on "Tuberculosis and Pregnancy." The opening speakers were Dr. G. S. Erwin and Dr. S. J. Barr.

Journal of Clinical Nutrition.—The first number of a new international journal on nutrition, the *Journal of Clinical Nutrition*, has now appeared from America. With Dr. S. O. Waife as its chief editor, it numbers Sir Edward Mellanby, F.R.S., and Dr. A. P. Meiklejohn among its corresponding editors. It will be published bi-monthly at a sterling subscription rate of 55s., post free, Messrs. Baillière, Tindall & Cox being the agents for it in the Commonwealth. Success for the new venture probably depends on the journal's ability to live up to its name. Lately, in some journals on nutrition, there has been a tendency for contributions on agricultural subjects to outnumber those with a medical bias. The new periodical could usefully help to restore the balance.

William Hyde Award.—Dr. Richard Scott has recently received the William Hyde Award for 1951, valued at £300, for his work with students at Edinburgh. The award is made from funds provided by the Nuffield Foundation in memory of the late Mr. William Hyde, who played a prominent part in the establishment of the Nuffield Provincial Hospitals Trust. Dr. Scott is physician in charge of the Royal Dispensary, Edinburgh, which is now used as a teaching general practice.

Emergency Bed Service: Applications and Admissions.—During the seven days ending February 23 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 1,472, of whom 84.29% were admitted. The yellow warning was cancelled from February 19, and the white warning was issued the same day.

Dr. C. E. Dent, reader in medicine in the University of London, is visiting the Universities of Florence and Rome for a week from March 3 under arrangements made by the British Council. He is to speak on chromatography.

Mr. John Foster, senior clinical lecturer in ophthalmology at Leeds University, has been invited to lecture at the University of Barcelona and at the Triennial Congress of Ophthalmology at Buenos Aires in April.

The closing date for applications for the **Anglo-French Exchange Bursaries** described recently in this column (see January 17, p. 169) is March 31.

COMING EVENTS

C.M.F./M.E.F. Physicians Reunion Dinner will be held on March 28 at Simpson's-in-the-Strand, with Dr. D. Evan Bedford in the chair. Further information can be obtained from Dr. A. Willcox, 59, Harley Street, London, W.1.

Laboratory Animals Bureau Congress.—The Sixth Laboratory Animals Bureau Congress is to be held at the Royal Veterinary College, London, N.W.1, on March 27 and 28. The congress, which will consist of three sessions, will be opened by Sir Harold Himsworth, and the chairmen at the three sessions will be Professor S. P. Bedson, F.R.S., Dr. R. Lovell, and Professor R. E. Glover respectively.

NEW ISSUES

British Journal of Ophthalmology.—The next issue (Vol. 37, No. 3) will be available in a week's time. The contents include:

CENTRAL AREOLAR CHOROIDAL SCLEROSIS. A. Sorsby and R. P. Crick.
CENTRAL SENILE AREOLAR CHOROIDAL SCLEROSIS: A HISTO-PATHOLOGICAL STUDY. Norman Ashton.
SPECTRAL SENSITIVITY CURVES AND THE ABSORPTION OF LIGHT BY THE OCULAR MEDIA. R. A. Weale.
OCULAR REACTION TO LENS PROTEIN: A PRELIMINARY STUDY. F. W. Law.
QUANTITATIVE STUDY OF VISUAL AFTER-IMAGES. C. A. Padgham.
MANDIBULO-FACIAL DYSOSTOSIS. A. H. Briggs.
SCLERAL RESECTION—LAMELLAR OR PENETRATION? C. Dee Shapland.
JOHN DALTON, F.R.S., D.C.L., LL.D., CAPTAIN JOSEPH HUDDART, F.R.S., AND THE HARRIS FAMILY. HISTORICAL NOTES ON CONGENITAL COLOUR BLINDNESS. J. W. Crerar and J. A. Ross.
INTRA-OCULAR OPERATIONS IN EGYPT. A. M. Girgis.
INJURY SIMULATING CONGENITAL ANOMALY. L. Stanton-Cook.

Issued monthly; annual subscription £4 4s., single copy 8s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

Details in this column are necessarily brief. Further information and tickets where required (marked ●) should be obtained from the institution concerned.

Monday, March 2

INSTITUTE OF NEUROLOGY.—5 p.m., Professor R. W. Russell: Comparative Study of the Effect of Electric Shock Convulsions on Behaviour.
MEDICAL SOCIETY OF LONDON.—8.30 p.m., Lettsomian Lecture by Dr. E. R. Cullinan: Some Disorders of the Liver and Bile Passages.

Tuesday, March 3

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor E. P. Sharpey-Schafer: Causes of Hypotension in Man.
●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. S. Thomson: Animal Diseases, etc.
WEST END HOSPITAL FOR NERVOUS DISEASES.—5.30 p.m., Dr. G. Parsons-Smith: Neurological demonstration.

Wednesday, March 4

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Animal Parasites in Dermatology.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. B. Larsen (Denmark): Occupational Deafness, Including Some Remarks on Auditory Fatigue and Adaptation.
INSTITUTE OF UROLOGY.—At St. Paul's Hospital, W.C., 4.30 for 5 p.m., Dr. C. Dukes: Pathology of Calculous Disease.
LIVERPOOL MEDICAL INSTITUTION.—At Manchester University, 5 p.m., joint meeting with Manchester Medical Society. Dr. E. N. Chamberlain: Rheumatic Carditis; Retrospect and Prospect; Mr. J. H. Hughes: Gastroscopy; a Retrospective Evaluation.
MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 8.15 p.m., joint meeting with Midland Counties Veterinary Association. Deficiency Diseases in Animals and Man.
OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Sir James Learmonth: Reflections on Portal Hypertension.

Thursday, March 5

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor G. W. Pickering: Natural History of Essential Hypertension.
FACULTY OF HOMOEOPATHY.—5 p.m., Dr. Grace H. Newell: Homoeopathy in Gynaecological Disorder.
●INSTITUTE OF CHILD HEALTH.—5 p.m., Dr. J. A. Fraser Roberts: Genetic Background of the Dull Child.
LONDON UNIVERSITY.—At St. Mary's Hospital Medical School, 5 p.m., Professor P. Mallet-Guy (Lyons): Les Opérations ...npathiques dans le Traitement des Pancréatites Chroniques Récidivantes (illustrated).
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.30 p.m., Otolaryngology Lecture by Professor E. C. Dodds: Biochemistry of Endolymph, Perilymph, and Cerebrospinal Fluid.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Dr. G. W. Corner: Embryology of Twins, Triplets, Quadruplets, and Quintuplets.
UNIVERSITY COLLEGE.—At Physiology Theatre, 4.45 p.m., public lecture by Professor V. B. Wigglesworth, F.R.S.: Chemical Aspects of Insect Physiology.

Friday, March 6

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. H. J. Wallace.
LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor G. F. Marrian, D.Sc., F.R.S.: Some Aspects of the Metabolism of the Steroid Hormones.
●ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS.—5 p.m., John Shields Fairbairn Memorial Lecture by Mrs. Ruth Graham (Boston, Mass.): Value of Vaginal Smear to the Gynaecologist.
ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., Mr. I. C. Menzies: Obesity.
ROYAL SANITARY INSTITUTE.—At Town Hall, Keighley, 10 a.m., Dr. H. M. Holt: Educational Aspects of a Clean Food Campaign; Mr. T. Lindsay: Some Practical Effects of a Clean Food Campaign.

Saturday, March 7

MIDLAND TUBERCULOSIS SOCIETY.—At Chest Clinic, 151, Great Charles Street, Birmingham, Professor Thomas McKeown: Inheritance and Environment in Tuberculosis.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—F. J. Hebbert, M.D., F.R.F.P.S., Assistant Physician (Geriatrics), Norwich and East Norfolk Area; G. McD. A. Turner, M.B., Ch.B., Medical Registrar, Newmarket General Hospital.

HENDERSON, WILLIAM GORDON, M.B., Ch.B., Junior Lecturer in Bacteriology, London Hospital Medical School.

O'CONNOR, MAURICE F. A., M.Ch., D.P.H., D.L.O., Assistant Ear, Nose, and Throat Surgeon, Jervis Street Hospital, Dublin.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—Brenda James, M.B., B.S., D.C.H., Paediatric Registrar, Southmead Hospital, Bristol; Stephanie Saville, M.B., B.Ch., Anaesthetic Registrar, Bath Group of Hospitals; A. Chalmers Fleming, M.B., B.S., Deputy Medical Superintendent, Hortham Hospital, Almondsbury, near Bristol; J. K. Trotter, M.R.C.S., L.R.C.P., D.A. (Part I), Anaesthetic Registrar, Frenchay Hospital, Bristol; W. Lumsden Walker, M.B., Ch.B., D.P.H., D.P.M., Senior Registrar in Psychiatry, Moorhaven Hospital, Ivybridge; C. E. C. Wells, M.B., B.S., M.R.C.P., Medical Registrar, Southmead Hospital; J. N. Hoffman, M.B., B.S., Registrar in Diseases of the Chest, Bristol Clinical Area; S. L. Paton, M.B., Ch.B., Registrar in Orthopaedic and Traumatic Surgery to Mount Gold Orthopaedic Hospital and to Traumatic Centre at the General Hospitals, Plymouth; R. A. Yorston, M.B., Ch.B., Registrar in Ear, Nose, and Throat Surgery to Bath Group of Hospitals.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Gray.—On February 9, 1953, at University College Hospital, London, W.C., to Jean (formerly Leader), wife of Dr. Ian Ramsay Gray, a daughter.
Jennett.—On February 20, 1953, at the Liverpool Maternity Hospital, to Sheila M. Pope, M.B., Ch.B., wife of Mr. W. Bryan Jennett, M.B., F.R.C.S., a son.
Turner Warwick.—On January 21, 1953, at the Middlesex Hospital, London, W., to Margaret (formerly Harvey Moore), M.R.C.P., wife of Richard Turner Warwick, F.R.C.S., a daughter.

DEATHS

Brown.—On February 4, 1953, at Woodbridge Hill, Guildford, Surrey, Osmond Hayman Brown, M.R.C.S., L.R.C.P., aged 59.
Browne.—On February 11, 1953, James M. Browne, M.B., B.Ch., D.O., of North House, Oakley Road, Bromley Common, Kent, aged 83.
Bunting.—On February 9, 1953, Gerald Lantsbery Bunting, M.D., of 16, Pembury Road, Worthing, Sussex, late of Tonbridge and Crowborough.
Cooke.—On February 3, 1953, at the Radcliffe Infirmary, Oxford, Edward Robert Cecil Cooke, M.C., M.R.C.S., L.R.C.P., of Little Milton, Oxford, aged 66.
Corsellis.—On February 8, 1953, at Glamis Lodge, Frinton-on-Sea, Essex, Ernest Shawe Corsellis, L.R.C.P.&S.I.
Gibson.—On January 27, 1953, John McCoy Gibson, M.B., B.Ch., D.O.M.S., of Mitcham Lane, Streatham, London, S.W., aged 77.
Grey.—On February 9, 1953, at Bristol, Harry Grey, M.D., formerly of Edinburgh, aged 83.
Hunt.—On February 6, 1953, Arthur Douglas Hunt, M.D., of 47, Wellington Road, Bournemouth, and late of Park Grange, Duffield Road, Derby, aged 72.
Jupp.—On February 8, 1953, at 6, Haven View Road, Seaton, Devon, Edgar Norman Jupp, M.R.C.S., L.R.C.P., aged 77.
Mann.—On January 30, 1953, in London, Dora Mann (Mrs. Clee), M.D., of 16, Salisbury Place, London, W., and Irwinleigh, Ascot, Berks.
Pain.—On January 25, 1953, in hospital, Thornhill Coles Pain, L.M.S.S.A., formerly of New Kent Road, London, S.E.
Petty.—On January 20, 1953, in Buenos Aires, Argentina, Michael Joseph Petty, O.B.E., M.D., F.R.C.S.
Stalkartt.—On January 31, 1953, at Kenilworth, Portsdown Hill Road, Cosham, Hants, Walter Henry Skinner Stalkartt, M.D., F.R.C.S.Ed., Surgeon Rear-Admiral, R.N., retired.
Thornett-Johnson.—On January 30, 1953, at 22, St. George's Road, St. Margaret's-on-Thames, Middlesex, Marian Thornett-Johnson, F.R.C.S.I.
Wylie.—On February 4, 1953, at 3, Hillway, Holly Lodge, Highgate, London, N., John Robert Wylie, M.B., B.S., D.M.R.E.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Is Penicillin Alone Enough for Syphilis?

Q.—*Is it true that penicillin alone is adequate treatment for syphilis in all stages? If not, what ancillary treatment is advised?*

A.—Many series of cases have so far been reported in which penicillin alone has proved to be adequate in the treatment of syphilis. In the small percentage of failures following treatment for primary or secondary syphilis there is much confusion about whether the reappearance of active lesions was due to reinfection or relapse. It is impossible to give a dogmatic opinion at this stage. Most workers in this country continue to give ancillary treatment consisting in one or two ten-week courses of bismuth, or one course of neoarsphenamine and bismuth. The writer gives one course of bismuth only.

The results obtained in neurosyphilis with penicillin combined with fever therapy are no better than with penicillin alone, but better results are claimed in the treatment of interstitial keratitis in young children with the concomitant administration of cortisone.

Diabetic Drivers

Q.—*Recent successful police prosecutions of diabetic motor-drivers suffering from hypoglycaemia due to insulin administration have prompted local road haulage depots to enquire whether they should continue to employ as drivers diabetics receiving insulin. (1) What advice should be given to the haulage depots? (2) What is the legal definition of a drug, and is insulin one? (3) What clinical or other criteria should be adopted in deciding whether an individual diabetic should be advised not to drive a car?*

A.—(1) Haulage depots should be advised to insist upon a medical examination of applicants for employment as drivers of haulage vehicles; ideally, a periodical re-examination of drivers should form part of the medical arrangements of each firm of contractors. Every applicant for employment as a motor-driver should in the first instance provide evidence from a medical practitioner on his fitness to drive a motor vehicle, and in default should be requested to submit himself to a medical examination by a practitioner nominated by the prospective employer. This examination would be conducted only when the prospective employer was satisfied with the candidate in all other respects: that is to say, the applicant would be appointed subject to passing a medical examination.

(2) There is no comprehensive legal definition of a drug. A drug is regarded as medicine for internal or external administration, and this definition would include insulin.

(3) This question has been to a large extent answered by a recent letter in the *Journal* from Dr. R. D. Lawrence (September 13, 1952, p. 616).

The most important consideration in deciding whether a diabetic is fit to drive a car is his ability to recognize hypoglycaemia in its earliest stages and to take the necessary steps to remedy it. In addition, he should always take his proper amount of carbohydrate food at the proper time, and never drive without adequate supplies of carbohydrate food in his car. Diabetics who are liable to frequent insulin reactions, and especially those in whom they are liable to occur without adequate warning, should be advised not to drive, both in their own interests and in that of the public.

Chloramphenicol Ointment in Blepharitis

Q.—*In the treatment of recurrent blepharitis by chloramphenicol ointment, is there any likelihood of either local sensitivity or drug-fastness developing?*

A.—Experience so far has not shown any local reactions to the use of 1% chloramphenicol ointment. As this preparation is not used, and need not be used, for any length of time the possibility of developing drug-fastness hardly arises. There seems to be no valid reason for using chloramphenicol for blepharitis, as this affection is generally due to Gram-positive organisms which respond well to penicillin ointment. No local remedy is completely satisfactory in blepharitis, for the general health is usually unsatisfactory, and recurrences are common unless this receives attention.

Oestrogens for Mumps Orchitis

Q.—*Is stilboestrol of value in the prevention and treatment of mumps orchitis? Hoyne, Diamond, and Christian[1] in the U.S.A. originally wrote in favour of it, but Candel[2] did not seem to think it worth while. Micks[3] says of it: "Clinical trials have not yet (1949) been extensive enough to prove or disprove this claim."*

A.—Little further work has been carried out on this form of therapy, and none of it is entirely satisfactory. There would appear to be no reason to expect oestrogen therapy to modify the course of a virus infection, and the best preventive measure against orchitis is probably the administration, where available, of convalescent serum or the gamma globulin prepared from it. When orchitis is established, efficient local cooling and support remain the most effective treatment.

REFERENCES

1 Hoyne, A. L., Diamond, J. H., and Christian, J. R. (1949). *J. Amer. med. Ass.*, **140**, 662.
2 Candel, S. (1951). *Ann. intern. Med.*, **34**, 20.
3 Micks, R. H. (1950). *Essentials of Materia Medica, Pharmacology, and Therapeutics* (5th edition). London.

Implantation of Hormone Pellets

Q.—*What is the technique of subcutaneous implantation of hormone pellets? How are the pellets sterilized?*

A.—The pellets are supplied already sterilized and each is contained in a sterile sealed tube between plugs of cotton-wool. With the aid of a file the tube is snapped across one of the plugs, which is removed, thereby withdrawing with it any minute particles of glass which may be present. The pellet should not be removed at this stage. Should the pellet become contaminated it may be sterilized by boiling in water in a test tube. The technique of injection is as follows:

Open or Incisional Method.—An incision 1 to 1¼ in. (2 to 4 cm.) in length is made in the subcutaneous tissue of the abdominal wall or of the infrascapular region. Strict asepsis is necessary, for sepsis, apart from its usual disadvantages, causes the pellets to be extruded. A small pocket, ½ to 1 in. (1 to 2 cm.) deep, is made by blunt-dissection in the subcutaneous tissue. The pellet is dropped into the pocket from its container and is gently pushed to the bottom with blunt forceps. If more than one pellet is to be implanted several pockets are made and a pellet is inserted into each. The wound is then closed with sutures.

Injector Method.—The injector is a blunt-ended or sharp-pointed trocar and a cannula of a bore just sufficiently wide to take a cylindrical pellet. The skin is cleaned, with a tenotomy knife a small incision is made slightly longer than the diameter of the cannula, and the trocar and cannula are pushed into the subcutaneous tissue at an angle of about 45 degrees. The trocar is withdrawn, and the pellet is dropped into the cannula from the container and gently pushed home with the trocar. If several pellets are to be inserted the position of the instrument should be changed slightly after each insertion so that they are separated from each other. The incision is closed with a suture.

Elliptical Pupils

Q.—*Why are the pupils of some animals oval instead of round?*

A.—In photography it is usual to reduce the aperture of the lens when it is required either to improve definition or to increase depth of focus. Usually the reduction of the aperture requires a longer exposure to be given because the image formed by the lens has suffered a loss of brightness. If photographs were being taken of objects the contour of which lay in a horizontal, or nearly in a horizontal, plane, then if increased definition or depth were required the usual method would be to use a smaller circular aperture and to increase the exposure as for normal subjects. There is, however, in this case an alternative method available—namely, to use an elliptical aperture with its long axis horizontal. Thus, suppose this to measure 8 mm. long by 2 mm. high, then the definition and depth for horizontal or nearly horizontal lines would correspond to those of a 2-mm. diameter circular aperture, but the light-transmitting power would correspond to that of a 4-mm. diameter circular aperture, since this has the same area as the ellipse. If photographs were wanted of objects with vertical contours, then the correct procedure would be to use an elliptical aperture with its long axis vertical. Similar reasoning applies to the eye, and those animals, like cats, to whom the outlines of tree trunks and the openings in fencing, etc., are important could with advantage have irises with elliptical apertures, the long axis being vertical. On the other hand, those animals, like cows, sheep, or goats, to whom the lie of the land is important could with advantage have the long axis of the ellipse horizontal.

Toxic Effects of Amphetamine

Q.—*What toxic effects may arise from prolonged use of dexamphetamine sulphate? I am particularly interested to know whether there is any risk of blood or hepatic changes, chronic dyspepsia, carcinogenesis, and such-like serious effects.*

A.—The actions and toxic effects of dexamphetamine sulphate are similar to those of amphetamine sulphate, but the D-isomer is claimed to be effective in smaller dosage. Both substances have been safely used for lengthy periods in narcolepsy or obesity in doses up to 60 mg. daily. The development of psychoses has been reported, as for example in the man of 49 who had taken 250 mg. daily for five years. Reports have also appeared of damage to bone marrow: panhaemocytopenia occurred in a girl of 21, and acute aplastic anaemia in a man of 26 who took 290 mg. during 19 days. Habituation may also occur, though this is probably not very common. Withdrawal symptoms observed included hallucinations, restlessness, and insomnia. These symptoms, together with anorexia, may be expected to follow prolonged administration in most patients. Many of those receiving amphetamine possess personality defects and may be especially prone to exhibit these side-effects. Tachycardia and hypertension have also been reported, but I am not aware of any evidence of carcinogenesis or liver damage from prolonged use of dexamphetamine.

Benign Prostatic Enlargement

Q.—*What is the cause of benign enlargement of the prostate?*

A.—The exact cause of benign enlargement of the prostate is not known, but it is probably related to hormonal imbalance. This is suggested by the fact that the enlargement begins to manifest itself most commonly at a period when testicular activity begins to decline. Other indications of the close association of testicular hormones with prostatic disease are provided by clinical evidence of the control of prostatic carcinoma by oestrogens and by castration, and the fact that while prostatic disease is quite common in dogs it does not occur in those which have been castrated.

It seems not improbable, therefore, that prostatic disease in man will eventually be treated, or at least prevented, by hormonal therapy, instead of by surgery, but at the present time the results of both androgenic and oestrogenic treatment are disappointing. We seem to be near the mark, but not quite there.

Khellin in Bronchospasm

Q.—*Is oral khellin effective in the treatment of bronchospasm? Are there any dangerous toxic effects which contra-indicate its use? Is it safe for children?*

A.—One of the pharmacological actions of khellin is a marked bronchodilator effect on guinea-pig bronchi.[1] Its clinical effect on humans is variable, but it can relieve bronchospasm, and its effect and that of adrenaline are, to a certain extent, additive. It is much more effective when given parenterally; the onset of its action is delayed and may be prolonged over 24 hours after a single intramuscular injection. The incidence of side-effects after oral use is only slightly lessened by using enteric-coated tablets, and in a recent trial[2] nausea, anorexia, and vomiting occurred in a high proportion of patients: nausea occurred in 65%—to a prohibitive degree in 32%, and sufficient to necessitate a suboptimal dose in 22%. The difficulty of maintaining an adequate dosage by the oral route limits the value of the drug, and for this reason it is inadvisable to give it to children.

REFERENCES
[1] Anrep, G. V., Barsoum, G. S., and Kenawy, M. R. (1949). *J. Pharm. Pharmacol.*, **1**, 164.
[2] Kennedy, M. C. S., and Stock, J. P. P. (1952). *Thorax*, **7**, 43.

NOTES AND COMMENTS

Troublesome Cough in a Child.—Dr. M. C. WATKINSON (Blackburn) writes: With regard to your question and answer on this subject ("Any Questions?" February 14, p. 413), troublesome night cough in children is one of the commonest problems I encounter in the baby clinics here, and I have worked out a rather homely method of treatment which rarely fails to be effective and which may help the doctor who made inquiry about the condition. First, I advise the mother to give drinks of lemon and honey (home prepared) to the child throughout the day and a spoonful of honey to be sucked slowly just as the child is going to bed. The bedroom window should be closed at least an hour before bedtime and kept closed during the night. Also, if possible, the room should be warmed by a small electric fire for 45 minutes or so before putting the child to sleep. The menthol rubbing ointments applied to chest and throat after the warm bath are helpful too. With my own children I find that this combination of therapies is usually sufficient, but if we hear the cough start during the night we switch on the electric heater for about half an hour, and as the room warms up again the cough ceases. Where, despite these measures, cough persists and is troublesome, I prescribe syrup of codeine phosphate according to Young's formula and using 2 drachms (7 ml.) as the adult dose. I did this at first with great trepidation after reading the Refresher Course article on "Acute Bronchitis" (*British Medical Journal*, 1951, **1**, 827). I find, however, that, as the author of the article stated, codeine is quite well tolerated by even small children. Certainly I should use it in preference to chloramphenicol.

Correction.—Mr. H. K. MCCOMB writes: With regard to your report in the medico-legal column (February 21, p. 461) concerning an action for negligence against "the surgical registrar" of Mayday Hospital, I would point out that there is more than one surgical registrar at that hospital.

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